Generic drugs: from bioequivalence to clinical equivalence

Dr. Nicola Ferri

University of Padova

Generic drugs: definition

A generic drug is bioequivalent to a brand name drug in dosage form, safety, strength, route of administration, quality, performance characteristics and intended use.

U.S. Food and Drug Administration

If two pharmaceutical forms are bioequivalent than their clinical efficacy and safety are, as definition, similar and can be utilized indistinctly from a therapeutic point of view (i.e. same therapeutic indications)

Generics

- Biopharmaceutical aspects

- Clinical Evidences

Bioequivalence: is a requirement imposed by FDA and EMA for in vitro and in vivo assays utilized for defining new pharmaceutical forms. For the marketing such requirement must be satisfied.

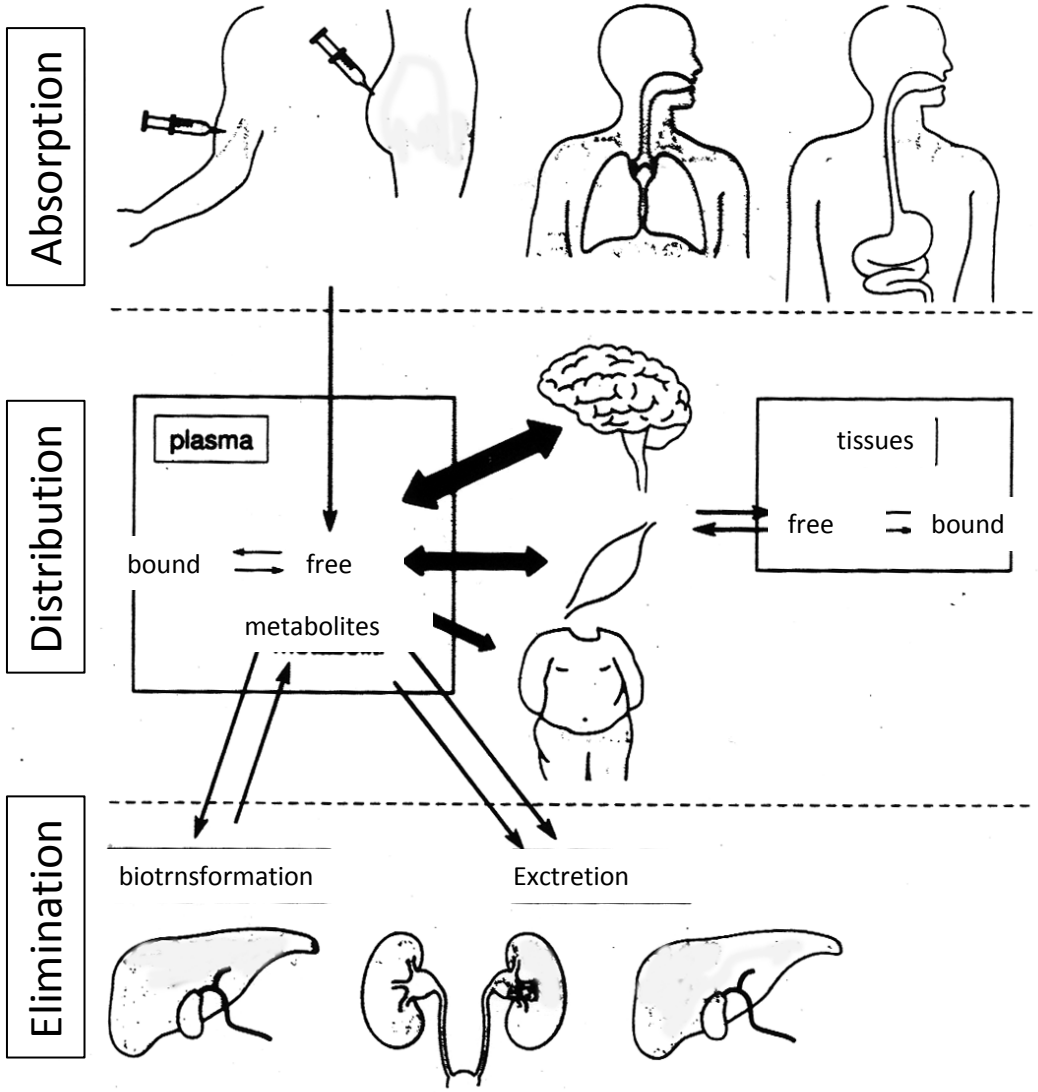
Bioequivalent pharmaceutical forms: They are forms that do not significantly differ in terms of speed and rate of absorption, when administered at the same molar dose and under similar experimental conditions.

Bioavailability (F)

- It is an index of rate and amount of the active component that is absorbed from a pharmaceutical form and reaches unmodified the systemic circulation.

- The magiority of the drugs is not completely available (effective dose) after oral administration.

ADME


Absorption
Distribution
Elimination
plasma
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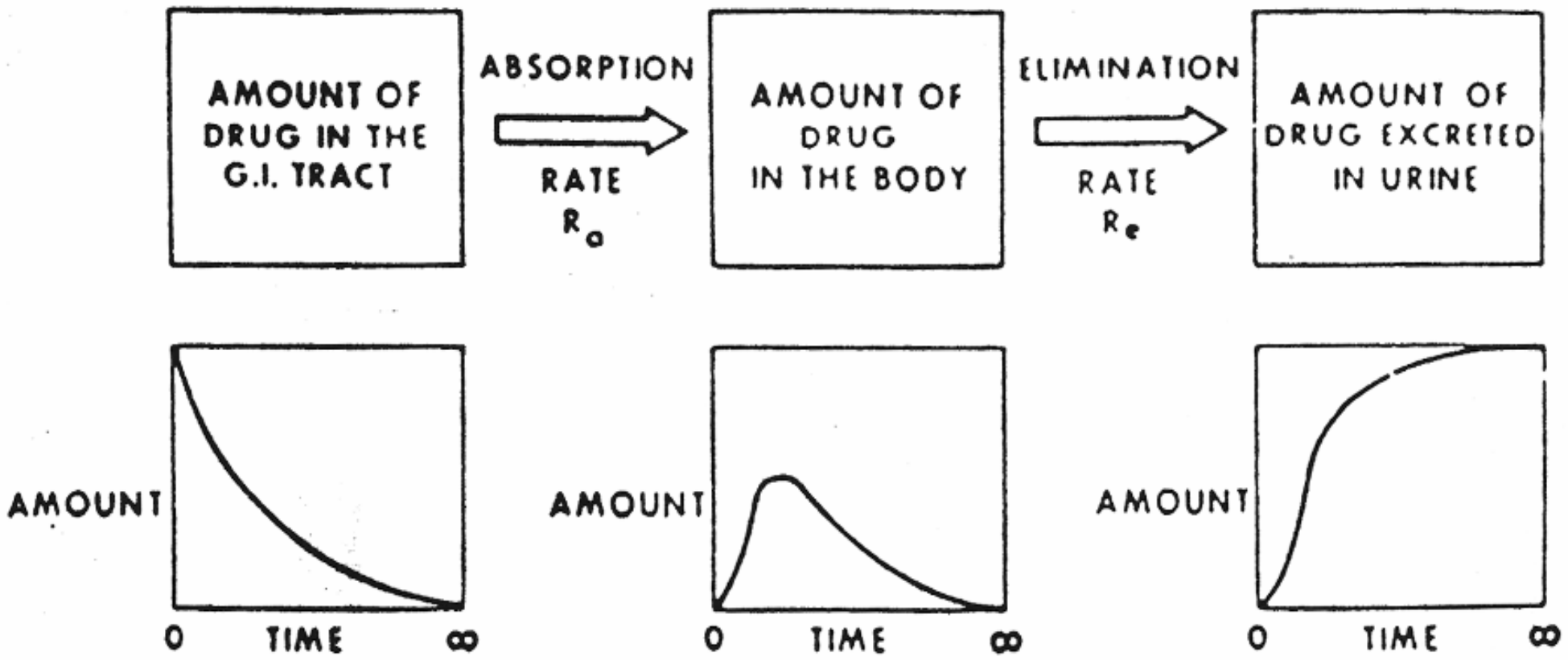
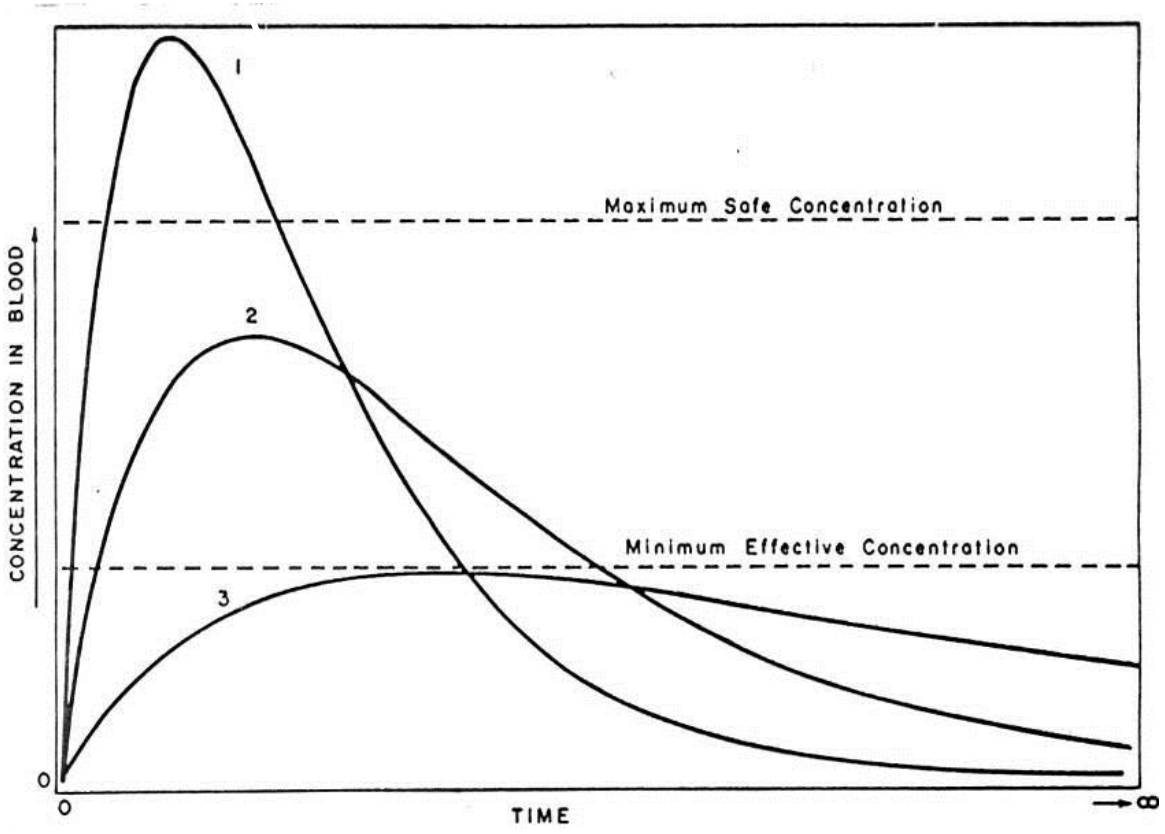
Exctretion

Pharmacokinetic profile after oral administration



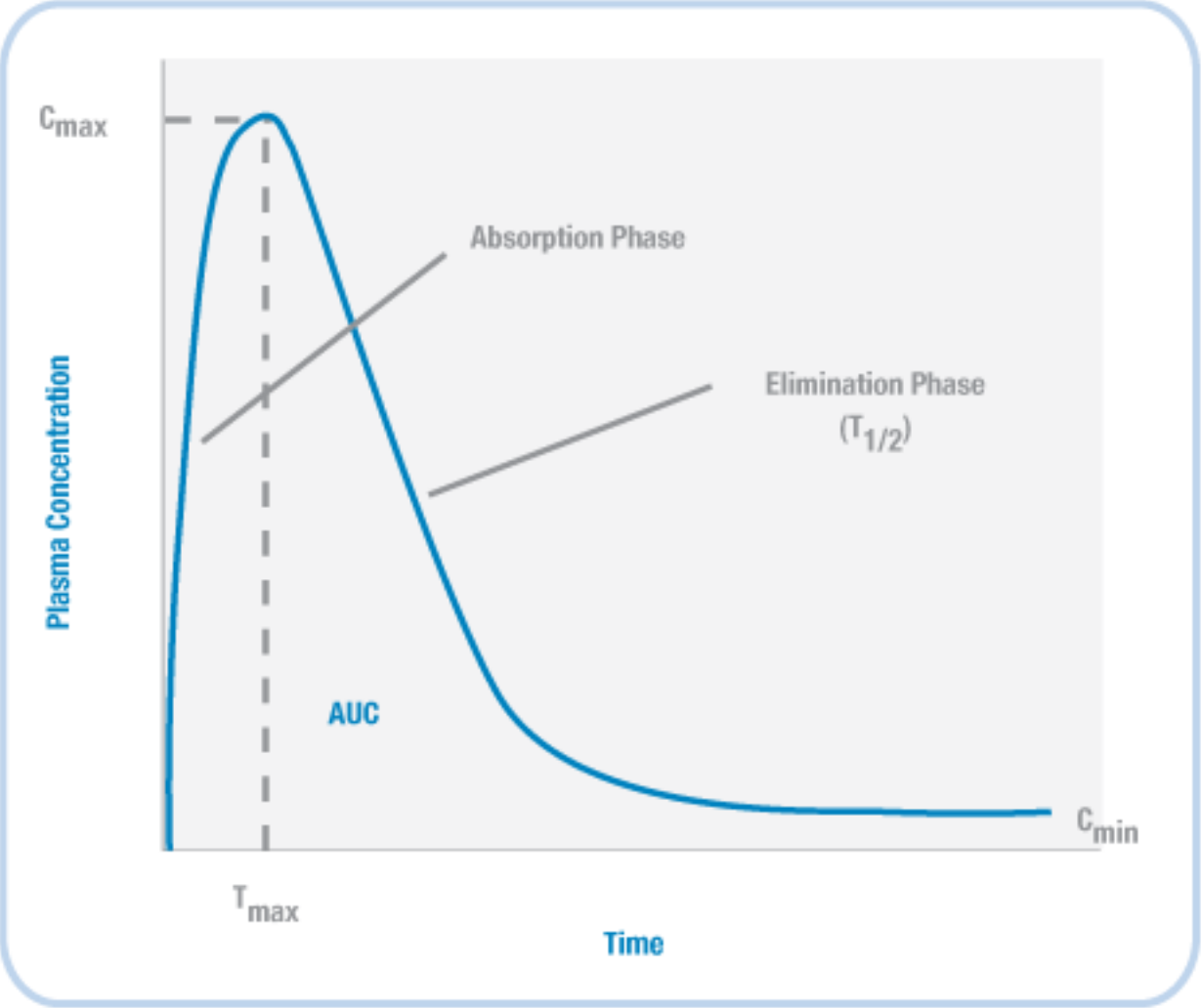
Profiles for drug in blood following equal extra vascular doses where elimination (k_2) is identical in all three cases



The generic drugs

- For receiving the registration of a generic drug, a product must present the data of pharmacokinetic parameters very similar to those of original pharmaceutical product.
- The three essential pharmacokinetic parameters are:
  - The maximal plasma concentration (Cmax);
  - The «area under the curve» (AUC), namely the trend of the plasma drug concentration in relation to the time, before its complete elimination;
  - The time required for reaching the maximal plasma concentration (Tmax).

The pharmacokinetic parameters



The generic drugs

- The guidelines indicate that the bioavailability of a tested drug can be accepted if the 90% confident range of Cmax and AUC is within 0,80 and 1,25 of that observed with the patent drug.

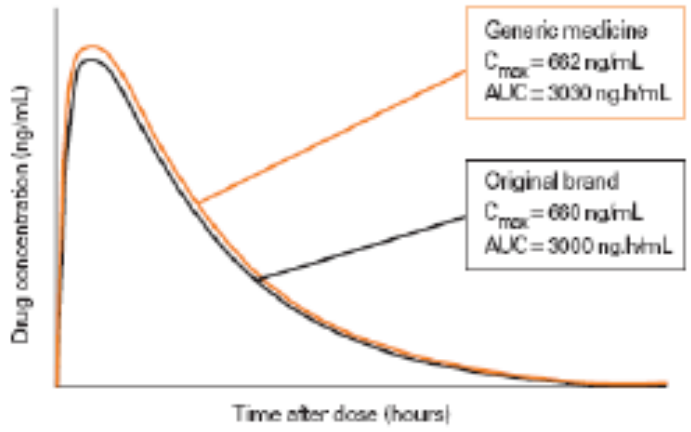
- The EMA and FDA guidelines also establish that for drugs with restricted therapeutic window, the range could be reduced.

Bioequivalence of drugs

Fig. 1

Bioequivalence analysis – a hypothetical bioequivalence study

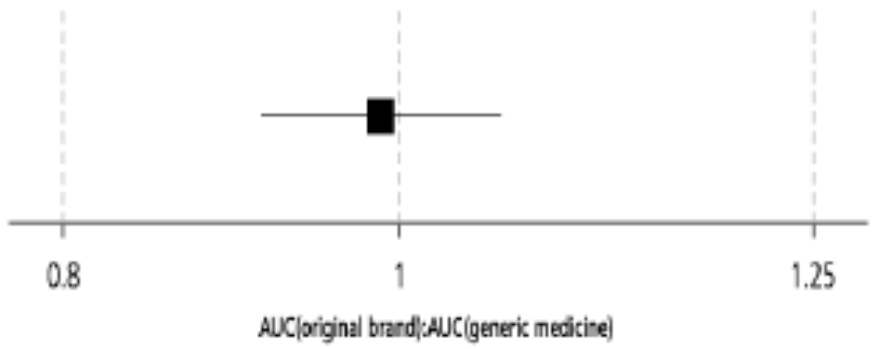
Mean concentration–time curves for two brands of a drug after single oral doses



The original brand:generic medicine ratio for AUC is 0.99 (90% CI 0.91 to 1.04) and for C_{max} is 0.99 (90% CI 0.92 to 1.07).

C_{max} peak plasma concentration
AUC area under the concentration–time curve
CI confidence interval

Reprinted with permission from NPS News 2006;44:3.



The marketed drug product that is approved by the FDA may not be the same formulation that was used in the original safety and efficacy clinical studies

Shargel L et al Applied Biopharmaceutics & Pharmacokinetics VI Edition 2012 McGraw Hill ED

Drug product performance

- New drug development may use a simple formulation such as a gelatin capsule containing the active ingredient diluted with lactose
- Since the initial safety and efficacy studies were performed using a different formulation the pharmaceutical manufacturer must demonstrate equivalent drug product performance to the original formulation
- **Equivalent drug product performance is generally demonstrated by an in vivo bioequivalence study in normal healthy volunteers**

Shargel L et al Applied Biopharmaceutics & Pharmacokinetics VI Edition 2012 McGraw Hill ED

STUDY DESIGN AND STUDY SUBJECTS

- In general, when comparing the bioavailability of a test (T) formulation to that of a reference (R) formulation, a randomized, two-period, two-sequence single dose crossover design is recommended.

- A parallel design may exceptionally be used in case of long half-life drugs.

SELECTION OF HEALTHY STUDY SUBJECTS

- It is now recommended that subjects should be 18 years or older (previously, between 18-55 years) and preferably have a Body Mass Index between 18.5 and 30 kg/m^2 (previously, within the normal range).

- This approach is considered adequate to allow extrapolation of the results to patient populations for which the reference medicinal product is approved.

- EMA guideline also clearly stated that “all treated subjects should be included in the analysis”.

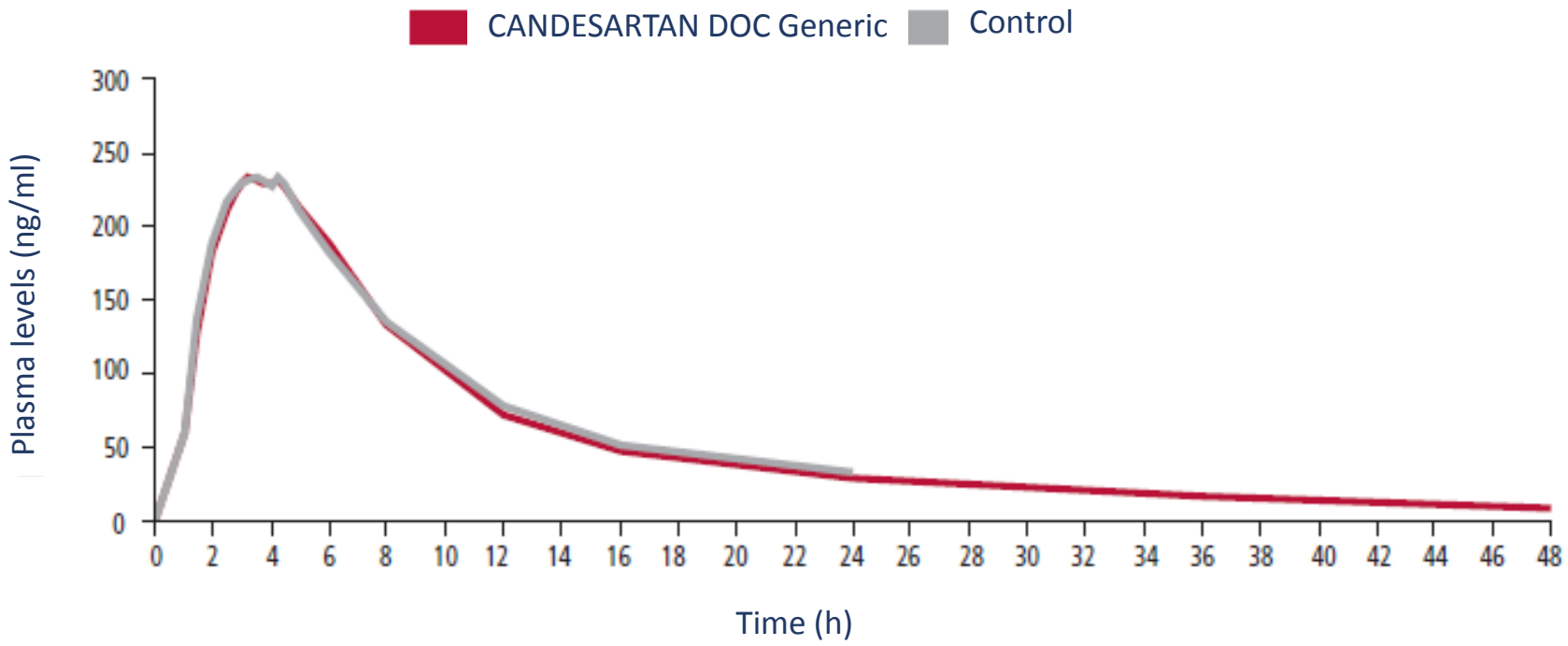
J Pharm Pharmaceut Sci (www.cspsCanada.org) 15(3) 376 - 388, 2012

Determination of bioequivalence of CANDESARTAN DOC Generic 32 mg tablets compared to originator (Control) (REGULATORY FILE)

INVESTIGATOR EXPERIMENTAL VENUE	Denis Audet, MD Anapharm, Québec, Canada
TREATMENTS	**CANDESARTAN DOC Generics** 32 mg tablets (1 tablet) **Control** 32 mg tablet (1 tablet)
STUDY DESIGN	**Randomized, crossover**
NUMBER OF SUBJECTS TREATED	**34 healthy volunteers**

Plasmatic values of candesartan for both formulations

PARAMETER	CANDESARTAN DOC Generic Average (±SD)	Control Average (±SD)
AUC (ng h/ml)	2726.70 (565.43)	2853.62 (742.54)
Cmax (ng/ml)	251.95 (77.98)	252.63 (105.13)
Tmax (h)	3.79 (1.09)	3.68 (0.99)
T1/2 (h)	13.42 (4.96)	12.93 (4.32)

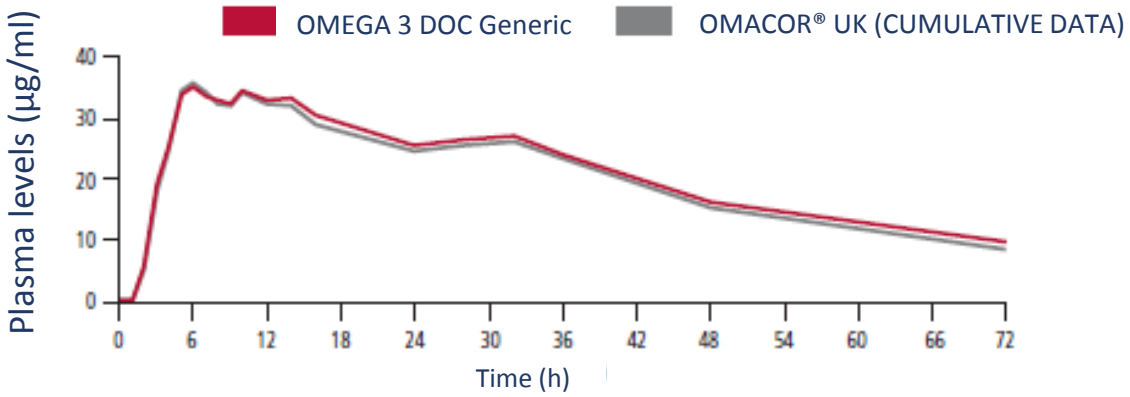


Determination of bioequivalence of OMEGA 3 DOC Generic 1000 mg soft capslues compared to originator (OMACOR® UK)

(REGULATORY FILE)

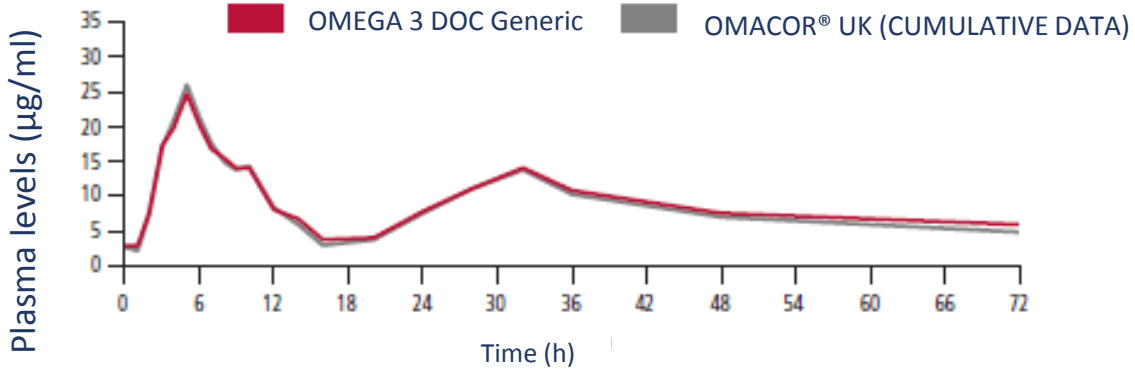
INVESTIGATOR EXPERIMENTAL VENUE	Xueyu (Eric) Chen, M.D., Ph.D., FRCP(C) Pharma Medica Research Inc., Toronto, Ontario, Canada
TREATMENTS	**OMEGA 3 DOC Generici** **1000 mg soft capsules (4 capsules)** **OMACOR®UK** **1000 mg soft capsules (4 capsules)**
STUDY DESIGN	**Randomized, crossover, 3 arms**
NUMBER OF SUBJECTS TREATED	**66 healthy volunteers**

Comparison of pharmacokinetic profile: Eicosapentaenoic acid (EPA)



PARAMETER	Eicosapentaenoic acid (EPA)	
	OMEGA 3 DOC Generic Average (CV%)	OMACOR® UK Average (CV%)
AUC (ng h/ml)	1461.47 (39)	1547.06 (36)
Cmax (ng/ml)	51.47 (42)	55.39 (37)
Tmax (h)	8.58 (62)	8.41 (64)

Comparison of pharmacokinetic profile: Docosahexaenoic acid (DHA)



PARAMETER	Docosahexaenoic acid (DHA)	
	OMEGA 3 DOC Generic Average (CV%)	OMACOR® UK Average (CV%)
AUC (ng h/ml)	599.75 (49)	628.66 (47)
Cmax (ng/ml)	35.02 (63)	36.25 (56)
Tmax (h)	9.34 (137)	8.19 (98)

Comparing generic and innovator drugs: a review of 12 years of bioequivalence data from the United States Food and Drug Administration

(Davit BM et al., Ann Pharmacother 2009; 43:1583-97)

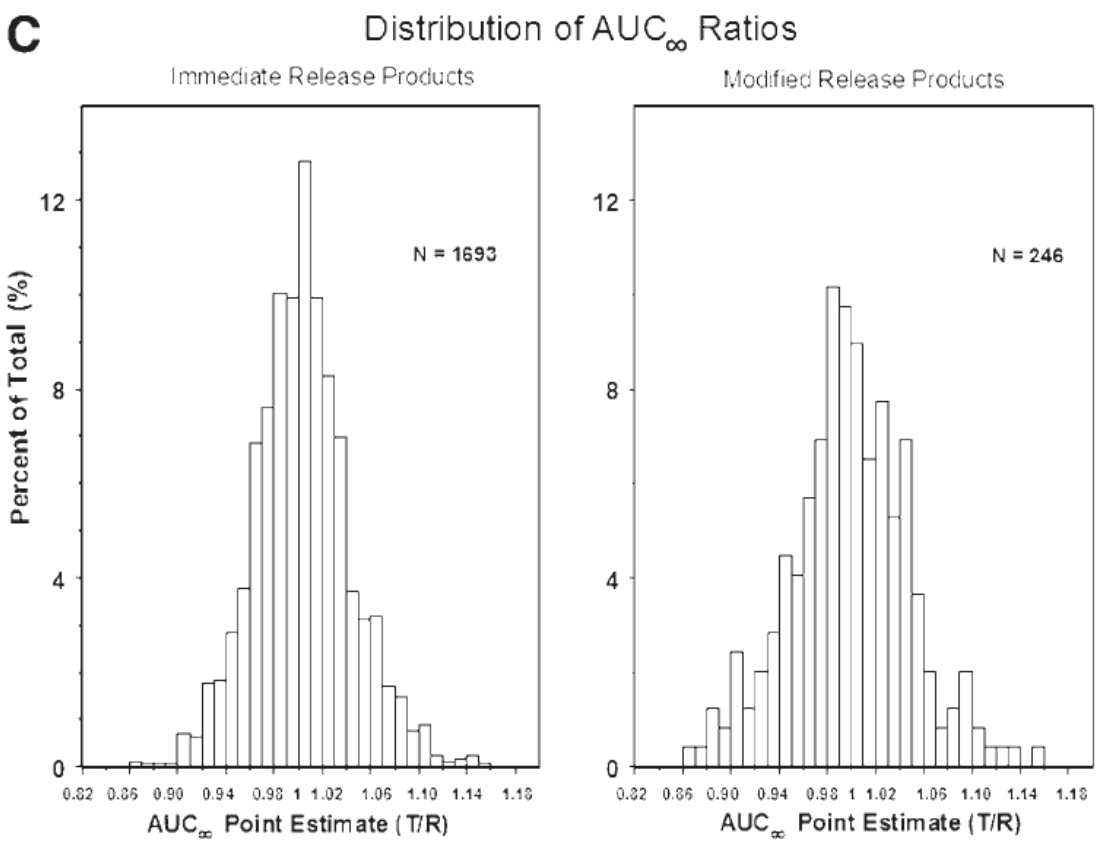
Table 3. Distribution of Percent Absolute Differences Between Generic and Innovator Bioequivalence Parameter Geometric Means

Range of Percent Differences	Percent of Total BE Studies (Studies, n)					
	All Drug Products (n = 2070)[a]		IR Drug Products (n = 1788)		MR Drug Products (n = 282)	
	C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}	C_{max}	AUC_{0-t}
0–5	64.1 (1327)	80.8 (1673)	66.1 (1182)	81.5 (1457)	51.4 (145)	76.3 (215)
6–10	27.5 (569)	16.8 (348)	26.2 (468)	16.3 (291)	36.2 (102)	19.8 (56)
11–15	8.0 (166)	2.3 (47)	7.3 (131)	2.1 (38)	12.1 (34)	3.5 (10)
>15	0.4 (8)	0.1 (2)	0.4 (7)	0.1 (2)	0.3 (1)	0.4 (1)

AUC = area under the concentration-time curve; BE = bioequivalence; C_{max} = peak drug plasma concentration; IR = immediate release; MR = modified release.

[a]Total number of studies in which the bioequivalence parameter was measured.

Comparing Generic and Innovator Drugs: A Review of 12 Years of Bioequivalence Data from the United States Food and Drug Administration



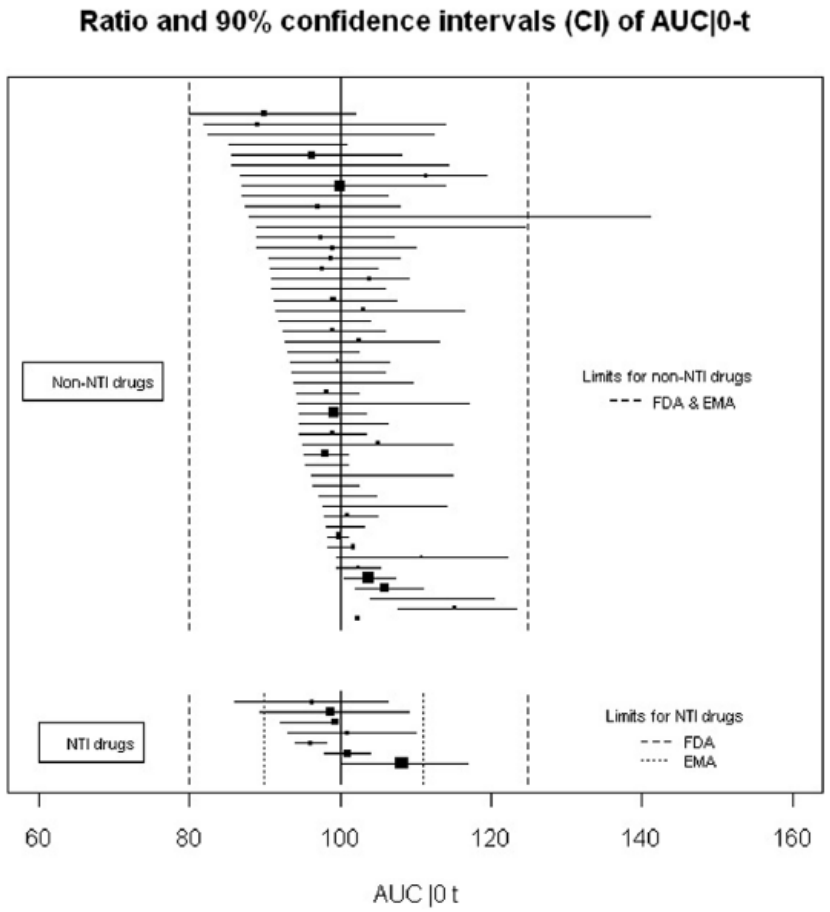
Histogram comparing distribution of test/reference bioequivalence parameter ratios for generic immediate-release and modified-release drug products

Davit BU et al The Annals of Pharmacotherapy n *2009 October, Volume 43* n **1583**

Ratio and 90% confidence intervals of AUC 0-t

NOT
Narrow therapeutic index

Narrow therapeutic index



Van der Meersch et al.
PLoS One
2011;6(8):e23611

Parent compound versus metabolites

The revised 2010 guideline is much clearer on the use of metabolites in bioequivalence assessment than the 2001 Note for Guidance.
It is now recommended that in almost all cases the evaluation of bioequivalence should be based upon the measurement of plasma concentrations of the parent compound.

Examples:
Enalaprilat/Enalapri
Perindiprilat/Perindopril
Zofenoprilat/Zofenopril
Glyceryldinitrate/Nitroglycerin
Oxypurinol/Allopurinol
Hydroxyflutamide/Flutamide
Acid metabolite/Terfenadine

J Pharm Pharmaceut Sci (www.cspsCanada.org) 15(3) 376 - 388, 2012

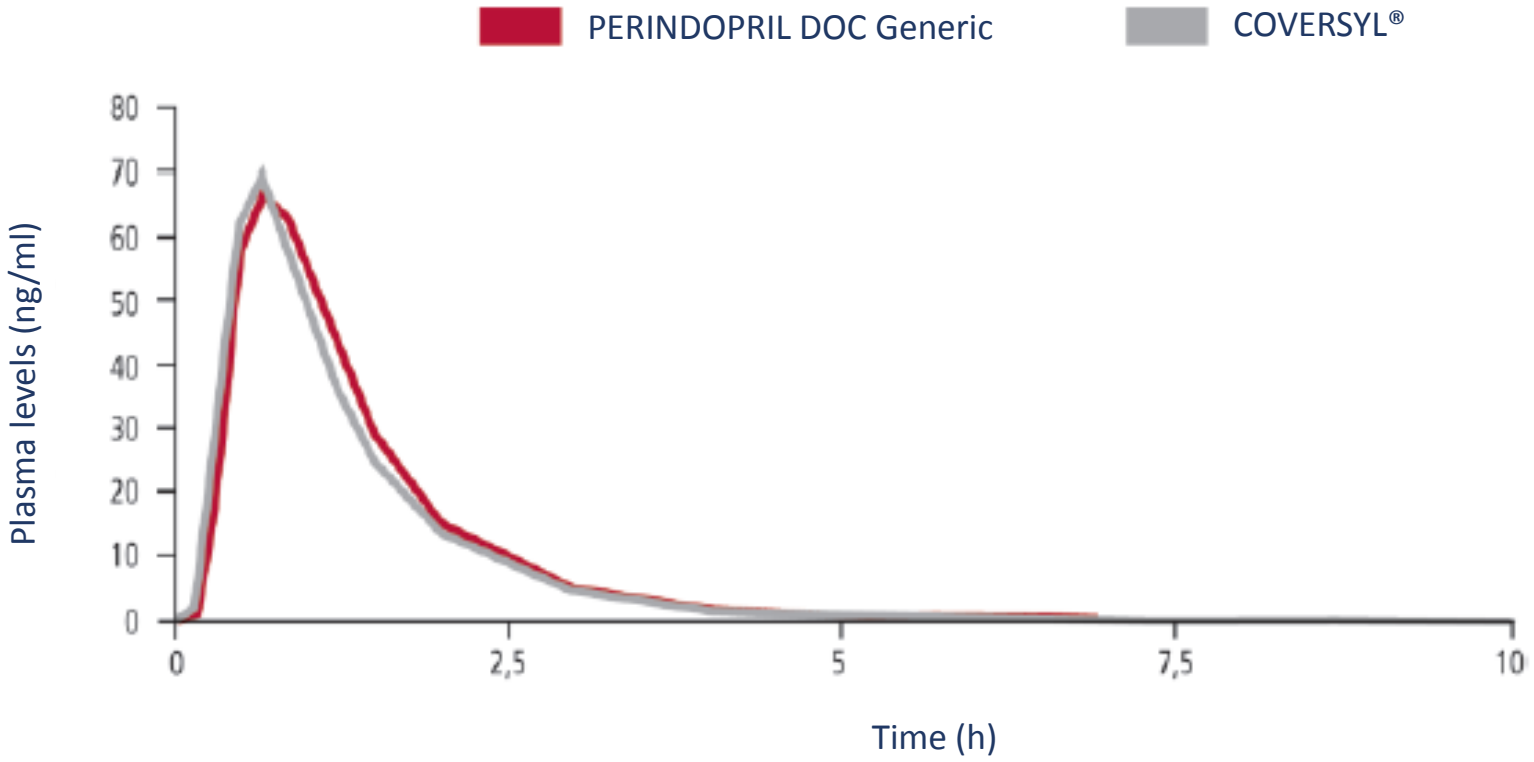
Determination of bioequivalence of PERINDOPRIL DOC Generic 8 mg tablets compared to originator (Coversyl®)

(REGULATORY FILE)

INVESTIGATOR EXPERIMENTAL VENUE	David Satok, MD, Chief Medical Officer Apotex Inc., Biomedical Division Toronto, Ontario,Canada
TREATMENTS	**PERINDOPRIL DOC Generics** 8 mg tablets (1 tablet) **Coversyl®** 8 mg tablet (1 tablet)
STUDY DESIGN	**Randomized, crossover**
NUMBER OF SUBJECTS TREATED	**26 healthy volunteers**

Plasmatic values of perindopril for both formulations

PARAMETER	PERINDOPRIL DOC Generic Average (±SD)	COVERSYL® Average (±SD)
AUC (ng h/ml)	89.246 (24)	87.163 (22)
Cmax (ng/ml)	75.481 (25)	73.022 (26)
Tmax (h)	0.66 (26)	0.66 (21)
T1/2 (h)	0.84 (4.96)	0.89 (22)



Generic drugs: definition

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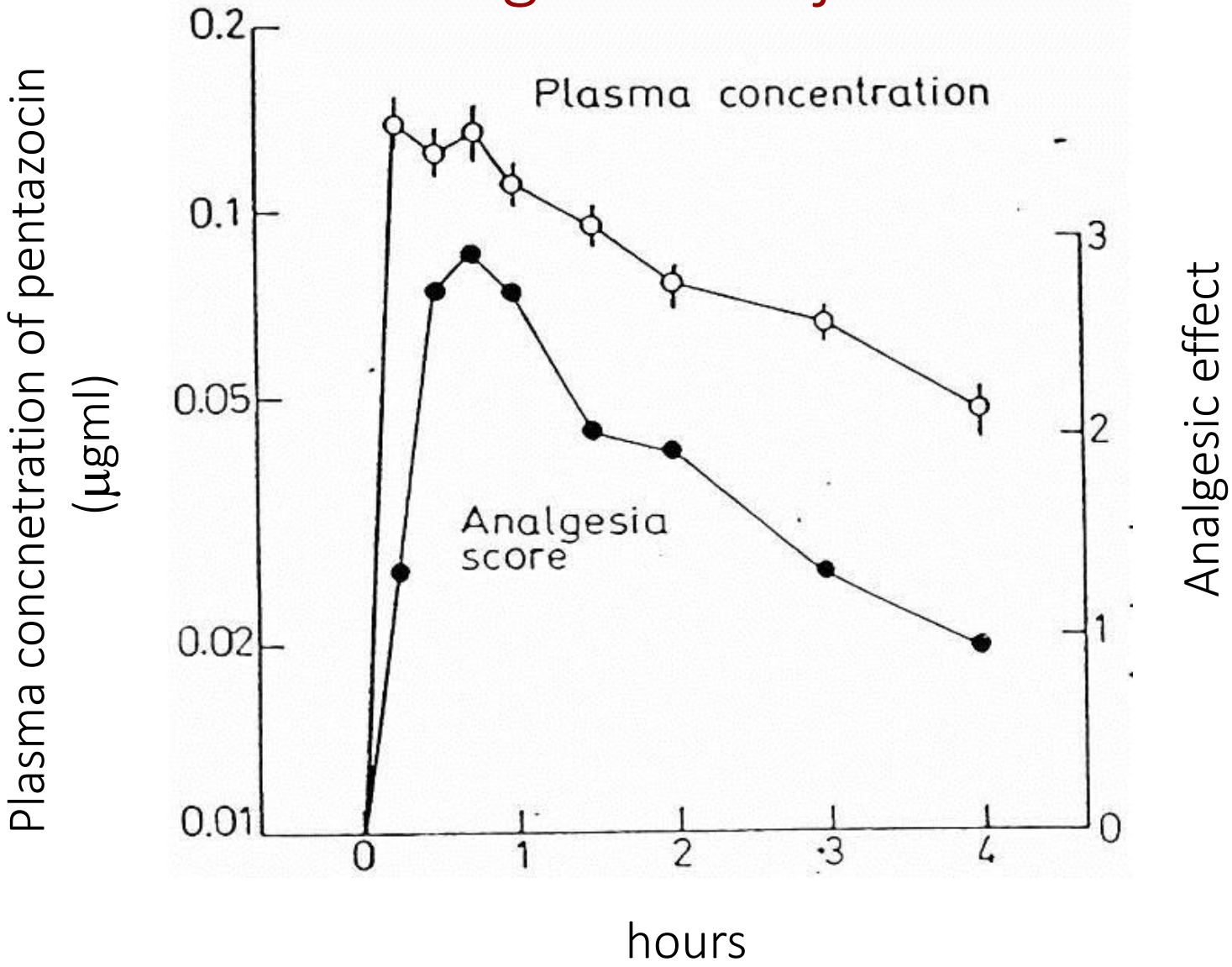
U.S. Food and Drug Administration

If two pharmaceutical forms are bioequivalent than their clinical efficacy and safety are, as definition, similar and can be utilized indistinctly from a therapeutic point of view (i.e. same therapeutic indications)

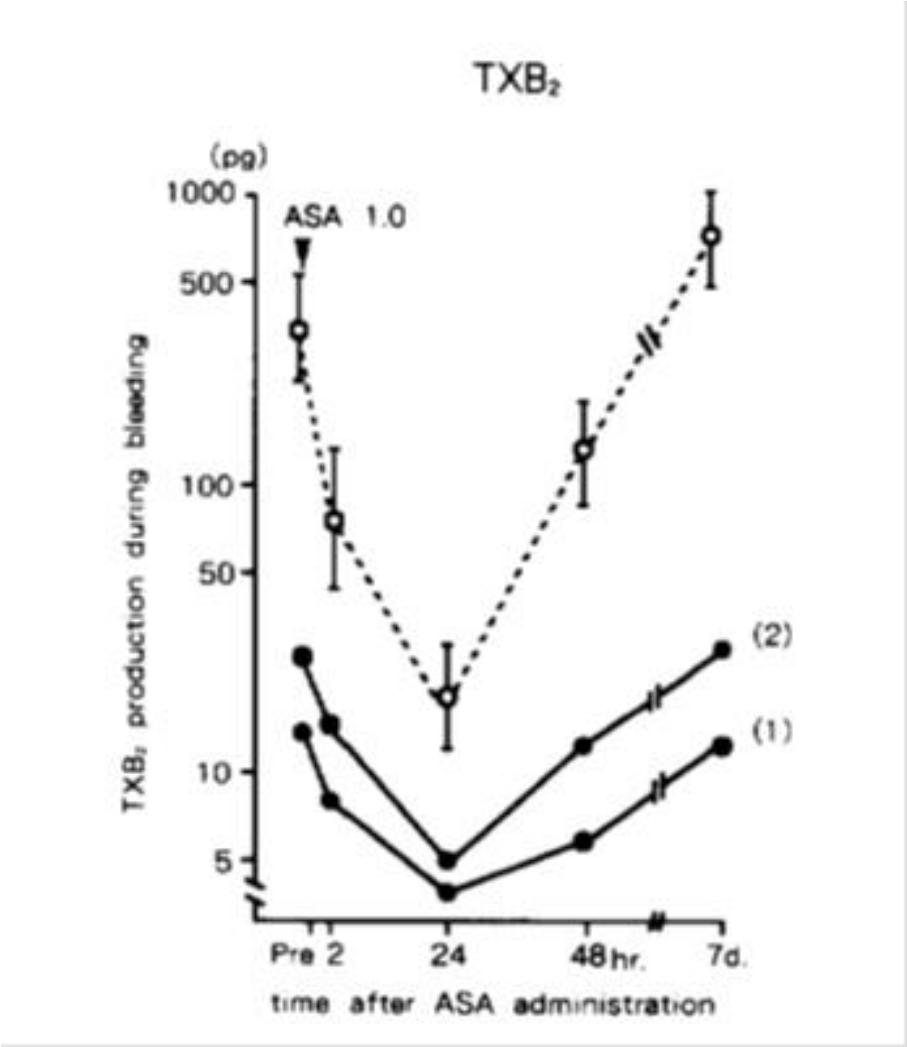
Plasma concentration of pentazocin and analgesic effect after a single i.m. injection of 0.64 mg



Ranges of therapeutic concentrations

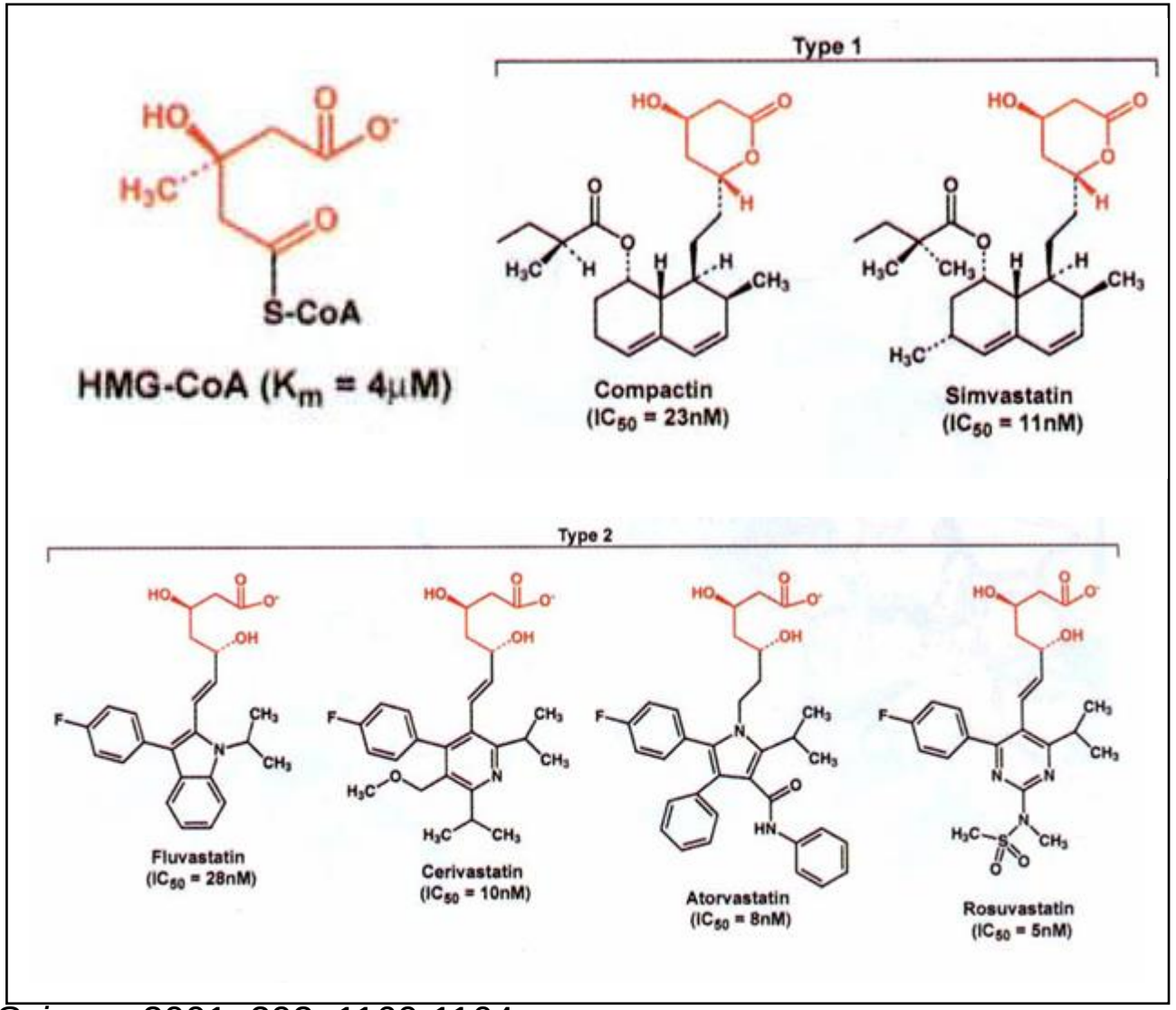
Drug	Disease	Therapeutic range
Carbamazepine	Epilepsy	4–12 μg/ml
Digoxin	Congestive heart failure	0.5–2.0 ng/ml
Disopyramide	Arrhythmias	3–5 μg/ml
Gentamicin	Infection	1–10 μg/ml
Lidocaine	Arrhythmias	2–6 μg/ml
Nortriptyline	Depression	50–150 ng/ml
Phenytoin	Epilepsy	10–20 μg/ml
Procainamide	Arrhythmias	4–8 μg/ml
Salicylic acid	Rheumatoid arthritis	10–30 mg/dl
Theophylline	Asthma	10–20 μg/ml

TXB_2 synthesis after aspirin treatment



Fuse I et al. Int J Hematol. 1996 Jun;63(4):317-24

Structural Formulas of HMG-CoA and of some Type 1 and Type 2 Statins



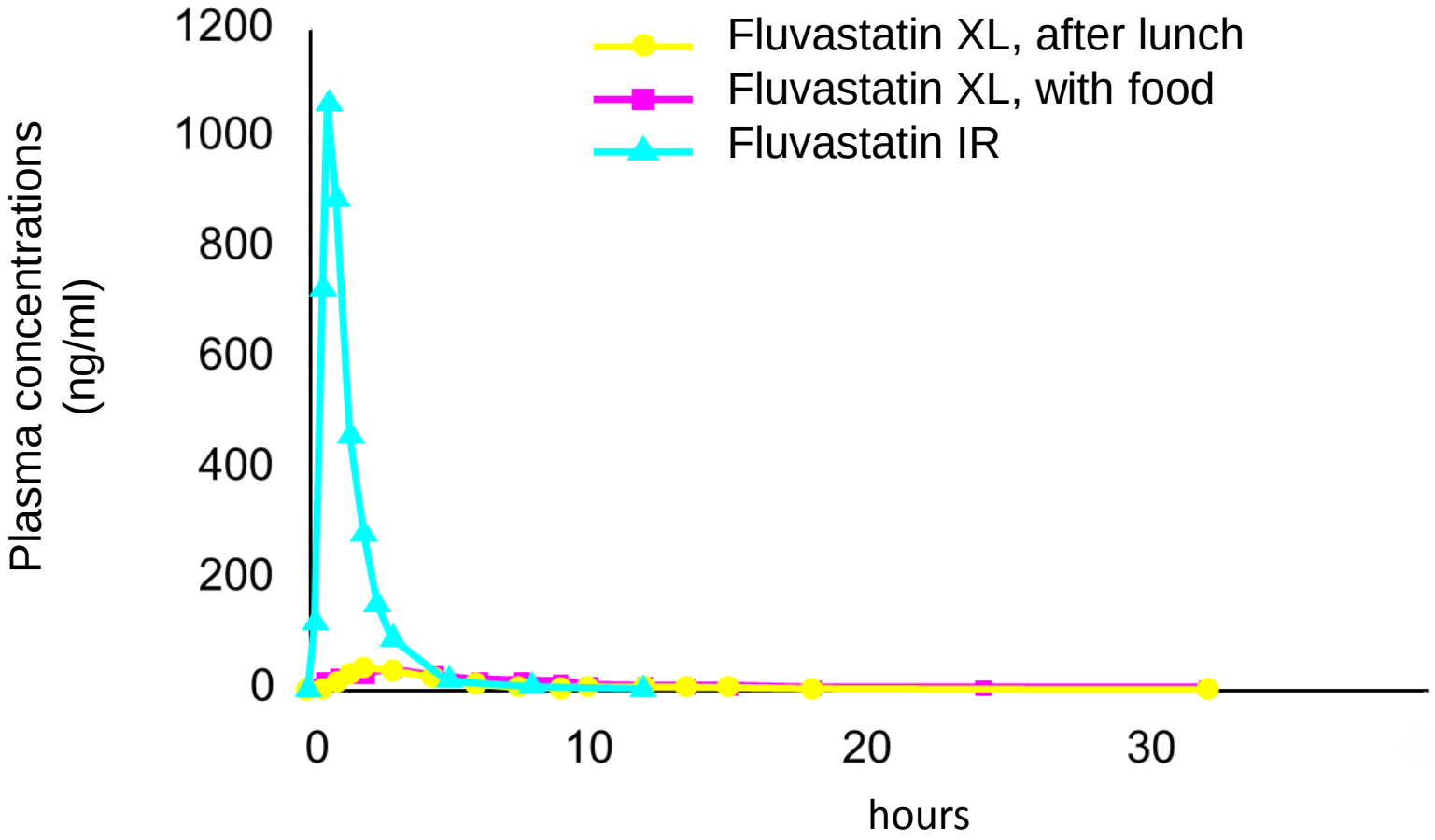
ES Istvan, J Deisenhofer *Science* 2001; 292: 1160-1164

Clinical Pharmacokinetics of Statins

Parameter	Atorva	Rosuva	Fluva	Fluva XL	Lova	Prava	Simva
Fraction absorbed (%)	30	50	98	98	30	34	60 - 80
T_{max} (hr)	2 - 3	3	0.5 - 1	4	2 - 4	0.9 - 1.6	1.3 - 2.4
C_{max} (ng/ml)	27 - 66	37	448	55	10 - 20	45 - 55	10 - 34
Bioavailability (%)	12	20	19-29	6	5	18	5
Effect of food	↓13%	↑ 20%	↓15% to ↑25%	0	↑50%	↓30%	0
Transporter proteins substrate	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Adapted from Corsini et al. 1999 *Pharmacol Ther* 84: 413-428

Systemic exposure after administration of fluvastatin XL (extended) or IR (immediate)



Appel-Dingemanse S, et al. Presented at: 29th European Symposium on Clinical Pharmacy; October 11-14, 2000; Basel, Switzerland

Clinical data from two independent trials submitted in 2001 for the market authorization showed comparable LDL-C lowering effects of fluvastatin ER 80 mg as compared to fluvastatin IR 40 mg bid

Study	Comparison	LS mean % change ER	LS mean % change IR	95% Confidence Interval	P-value Superiority	P-value Non-Inferiority
XUOF302	Lescol® XL 80 mg vs. Lescol® 40 mg bid	-32.6 .	-32.7	-2.4, 2.7	0.928	<0.001*
XUOF353	Lescol® XL 80 mg vs. Lescol® 40 mg bid	-33.3 .	-30 .7	-5.9, +0.9	0.144	<0.001*

BMC Clinical Pharmacology

BioMed Central

Research article

LDL-cholesterol lowering effect of a generic product of simvastatin compared to simvastatin (Zocor™) in Thai hypercholesterolemic subjects – a randomized crossover study, the first report from Thailand

Viroj Wiwanitkit MD*[1], Danai Wangsaturaka MD[2] and Oranee Tangphao MD[3]

BMC Clin Pharmacol. 2002;2:1.

Table 2: Characteristics of the subjects in both groups after taking drugs for 8 weeks

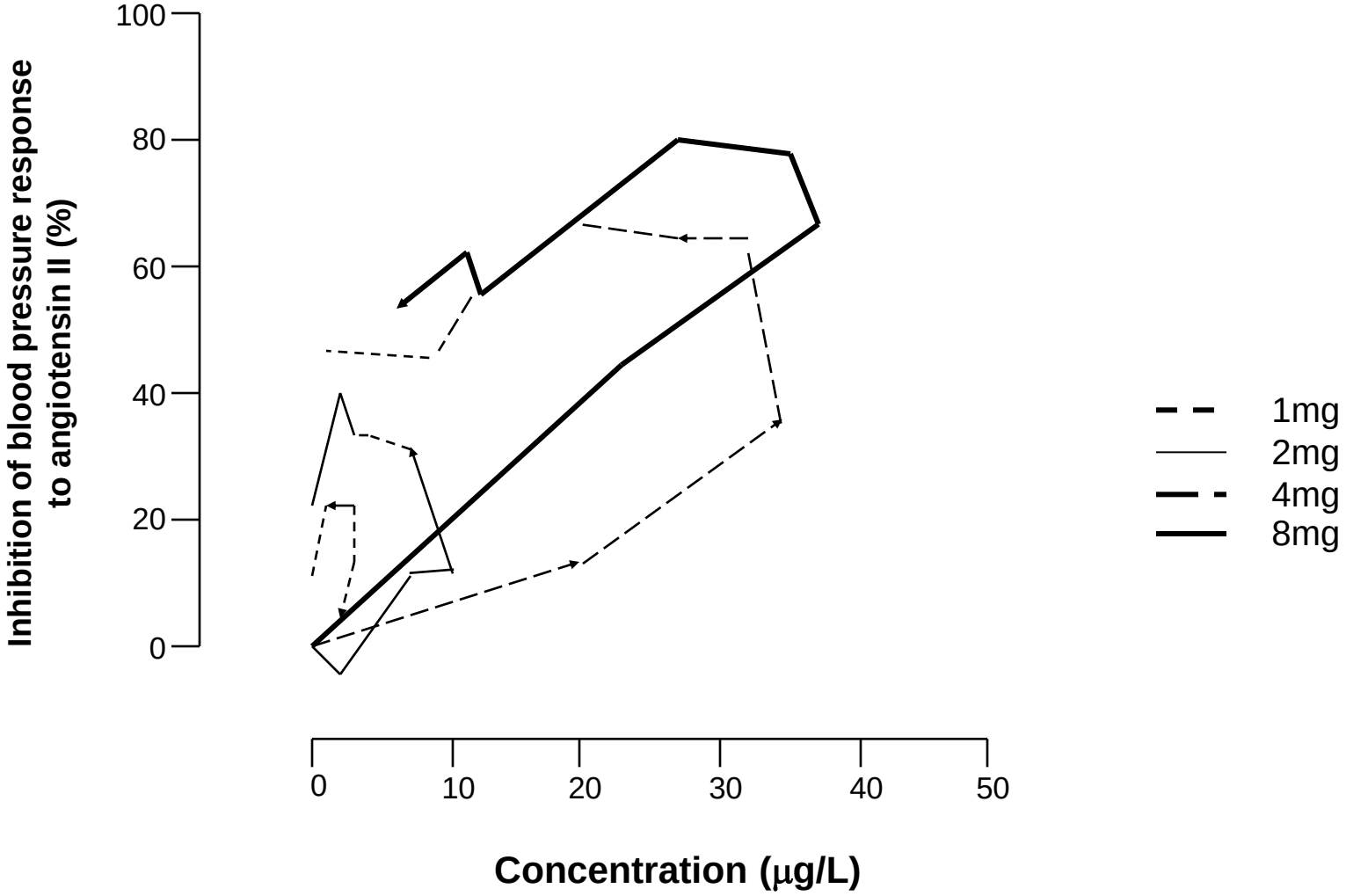
Parameters	mean ± standard deviation (90 % confidence interval)		P-value
	1st group (N = 22)	2nd group (N = 19)	
Total cholesterol (mg/dL)	191.80 ± 37.41 (178.37–205.23)	198.90 ± 31.48 (187.02–210.78)	NS
HDL (mg/dL)	45.50 ± 8.38 (42.49–48.51)	50.80 ± 10.49 (46.84–54.76)	NS
Triglyceride (mg/dL)	140.90 ± 69.49 (115.96–165.84)	129.20 ± 78.59 (99.54–158.86)	NS
LDL (mg/dL)	118.20 ± 30.92 (107.10–129.30)	122.30 ± 22.43 (113.84–130.76)	NS

Table 3: Characteristics of the subjects in both groups after crossover and continuation of drug for further 8 weeks

Parameters	mean ± standard deviation (90 % confidence interval)		P-value
	1st group (N = 21)	2nd group (N = 16)	
Total cholesterol (mg/dL)	200.30 ± 36.86 (187.07–213.53)	182.40 ± 17.24 (175.31–189.49)	NS
HDL (mg/dL)	47.40 ± 9.64 (43.94–50.86)	49.40 ± 10.38 (45.13–53.67)	NS
Triglyceride (mg/dL)	142.40 ± 62.54 (119.95–164.85)	127.40 ± 58.40 (103.38–151.42)	NS
LDL (mg/dL)	124.40 ± 31.70 (113.02–135.78)	107.50 ± 14.65 (101.48–113.52)	NS

BMC Clin Pharmacol. 2002;2:1.

Hysteresis loop of once daily treatment with candesartan



Gleiler CH et al., Drug Disposition 2002;41(1):7-17

- The measure of plasma concentrations have allowed to study the pharmacological effects of an active component, and today represents the experimental tool better characterized for the determination of generic drugs

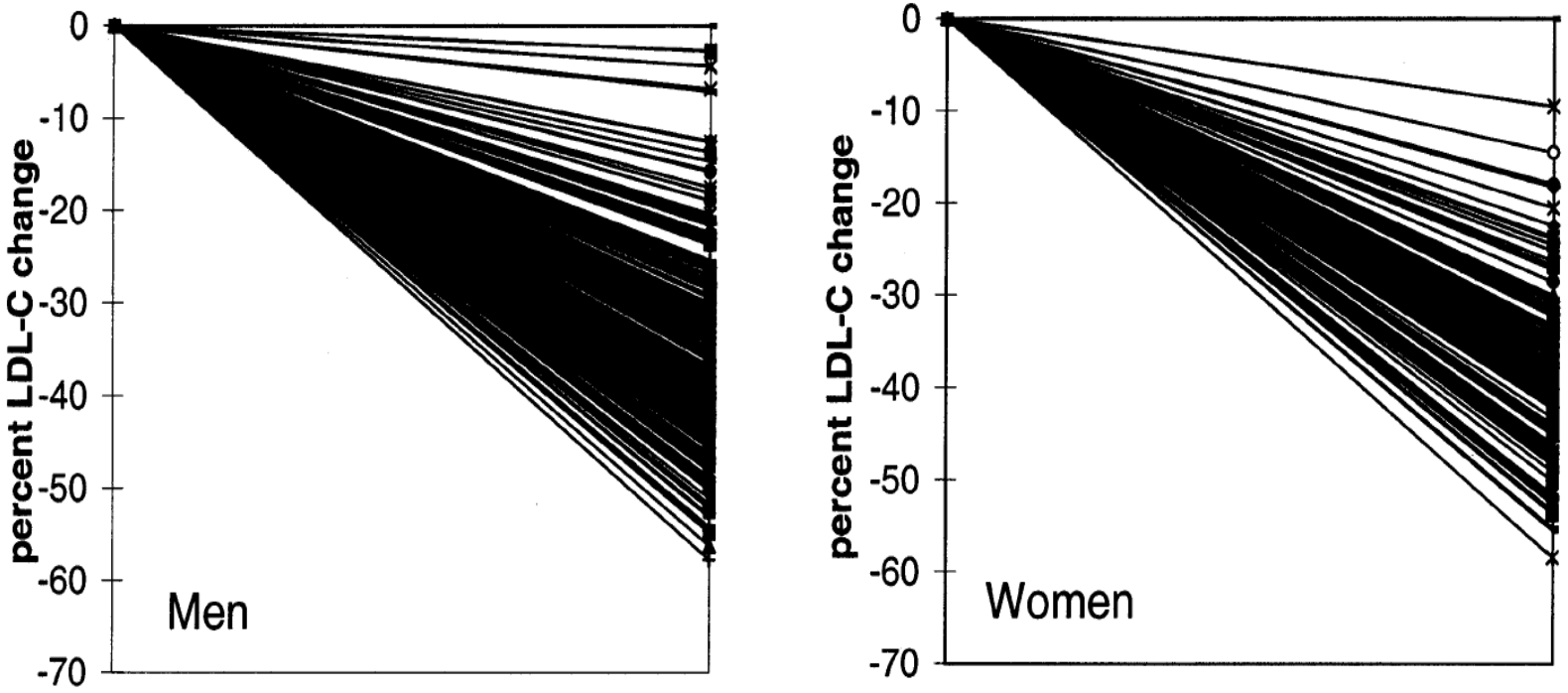
- The bioequivalent studies represent an important approach for the characterization of a generic drug with the awareness of the potential limits of this method (i.e. lack of direct relationship between the pharmacokinetic profile and pharmacodynamic action)

Generics

- Biopharmaceutical aspects

- Clinical equivalence

Individual LDL-C % Response to Atorvastatin 10mg/day



JAMA®

Online article and related content current as of December 5, 2008.

Clinical Equivalence of Generic and Brand-Name Drugs Used in Cardiovascular Disease: A Systematic Review and Meta-analysis

Aaron S. Kesselheim; Alexander S. Misono; Joy L. Lee; et al.

JAMA. 2008;300(21):2514-2526 (doi:10.1001/jama.2008.758)

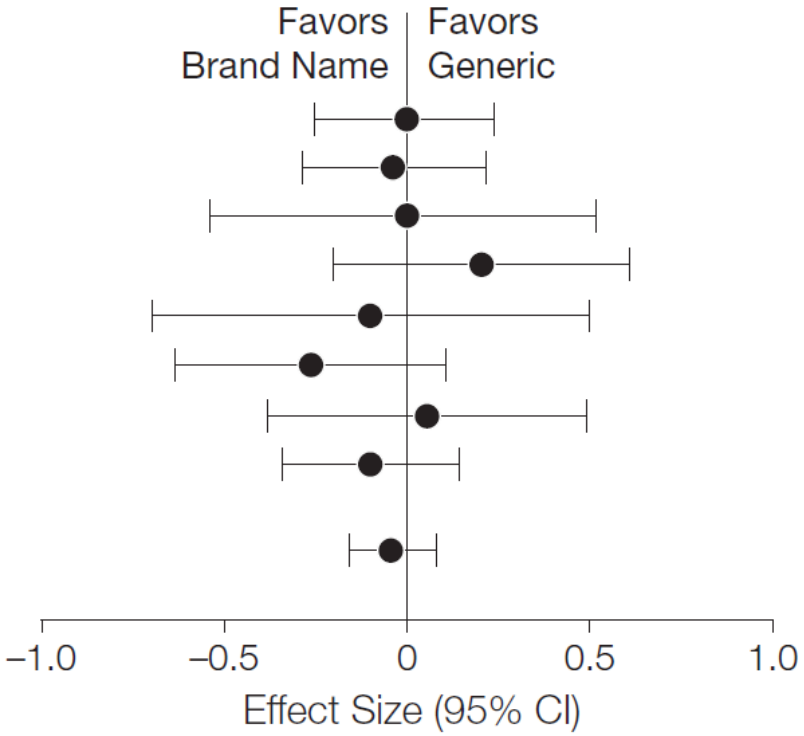
Context Use of generic drugs, which are bioequivalent to brand-name drugs, can help contain prescription drug spending. However, there is concern among patients and physicians that brand-name drugs may be clinically superior to generic drugs.

Study Selection Studies compared generic and brand-name cardiovascular drugs using clinical efficacy and safety end points.

Conclusions Whereas evidence does not support the notion that brand-name drugs used in cardiovascular disease are superior to generic drugs, a substantial number of editorials counsel against the interchangeability of generic drugs.

Drug Class and Meta-analyses of Trials Comparing Generic and Brand-Name Drugs in Cardiovascular Disease

Drug Class	No. Studies	No. Subjects	Effect Size (95% CI)
β-Blockers	6	135	0.00 (–0.24 to 0.25)
Diuretics	10	135	–0.03 (–0.28 to 0.22)
Calcium channel blockers	4	242	0.00 (–0.53 to 0.53)
Antiplatelet agents	2	50	0.21 (–0.19 to 0.61)
ACE inhibitors	1	23	–0.09 (–0.68 to 0.50)
Statins	2	71	–0.25 (–0.62 to 0.12)
α-Blockers	1	43	0.06 (–0.37 to 0.50)
Warfarin	4	138	–0.09 (–0.33 to 0.15)
Overall	30	837	–0.03 (–0.15 to 0.08)



JAMA. 2008;300(21):2514-2526

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PLOS | ONE

Off-Patent Generic Medicines vs. Off-Patent Brand Medicines for Six Reference Drugs: A Retrospective Claims Data Study from Five Local Healthcare Units in the Lombardy Region of Italy

Giorgio L. Colombo[1,2]*, Enrico Agabiti-Rosei[3], Alberto Margonato[4], Claudio Mencacci[5], Carlo Maurizio Montecucco[6], Roberto Trevisan[7]

1 Department of Drug Sciences, University of Pavia, Pavia, Italy, **2** S.A.V.E. Studi Analisi Valutazioni Economiche, Milan, Italy, **3** Division of Medicine and Surgery, Spedali Civili, Brescia, Italy, **4** Division of Cardiology, San Raffaele University Hospital, Milan, Italy, **5** Department of Neuroscience, A.O. Fatebenefratelli e Oftalmico, Milan, Italy, **6** Division of Rheumatology, IRCCS Policlinico S Matteo, University of Pavia, Pavia, Italy, **7** Unit of Diabetology, Ospedali Riuniti di Bergamo, Bergamo, Italy

Hospitalizations in persistent patients (mean number of hospitalizations)

	Type	No.	Min	ASL associated with min	Max	ASL associated with max	Mean Diff.	SD	CI 95% Low. Lim.	CI 95% Upp. Lim.	p-value
Metformin	Branded	1408	1.13	Lecco	1.33	Pavia	0.03	0.02	−0.01	0.07	N.S.
A10BA02	Generic	1490	1.20	Bergamo	1.28	Lecco e Pavia					
Amlodipine	Branded	3832	1.26	Melegnano	1.31	Pavia e Milano city	−0.02	0.03	−0.07	0.04	N.S.
C08CA01	Generic	677	1.18	Lecco	1.32	Pavia e Bergamo					
Simvastatin	Branded	1657	1.20	Lecco	1.28	Milano city	−0.01	0.02	−0.05	0.03	N.S.
C10AA01	Generic	1391	1.21	Pavia	1.29	Lecco e Melegnano					
Sertraline	Branded	310	1.14	Pavia	1.26	Lecco	−0.04	0.04	−0.13	0.04	N.S.
N06AB06	Generic	313	1.06	Lecco	1.47	Pavia					
Propafenone	Branded	127	1.00	Pavia	1.40	Melegnano	−0.03	0.06	−0.14	0.08	N.S.
C01BC03	Generic	101	1.00	Melegnano	1.50	Pavia					
Alendronate	Branded	310	1.07	Lecco	1.30	Milano city	0.002	0.04	−0.08	0.08	N.S.
M05BA04	Generic	234	1.12	Melegnano	1.31	Bergamo					

ASL: Local Healthcare Units. ASLs enrolled: Milano city; Lecco; Bergamo; Pavia; Milano2.
N.S. not statistically significant.
doi:10.1371/journal.pone.0082990.t004

Plos one December 2013
| Volume 8 | Issue 12 |
e82990

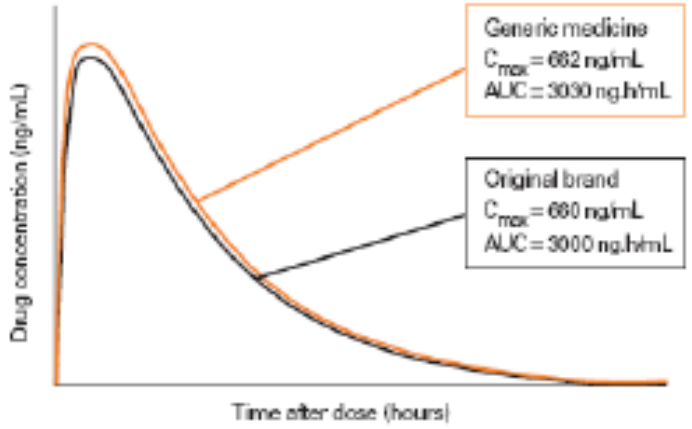
from bioequivalence

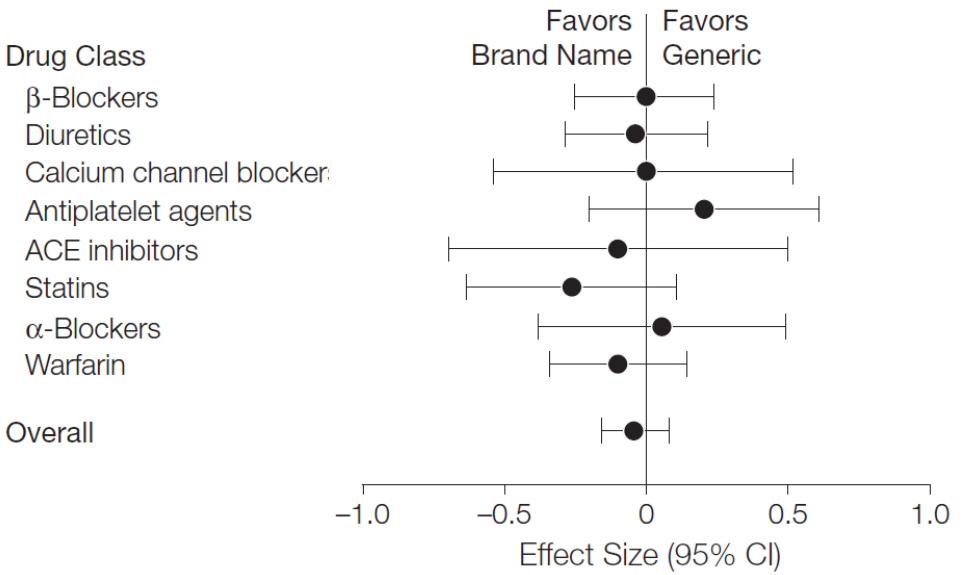
to

clinical equivalence

Bioequivalence analysis – a hypothetical bioequivalence study

Mean concentration–time curves for two brands of a drug after single oral doses





Generics

- Biopharmaceutical aspects
- Clinical equivalence
- Real clinical practice

Medication persistence and the use of generic and brand-name blood pressure-lowering agents

Giovanni Corrao[a], Davide Soranna[a], Carlo La Vecchia[b,c,d], Alberico Catapano[e,f], Enrico A. Rosei[g], Gianfranco Gensini[h], Luca Merlino[i], and Giuseppe Mancia[j,k]

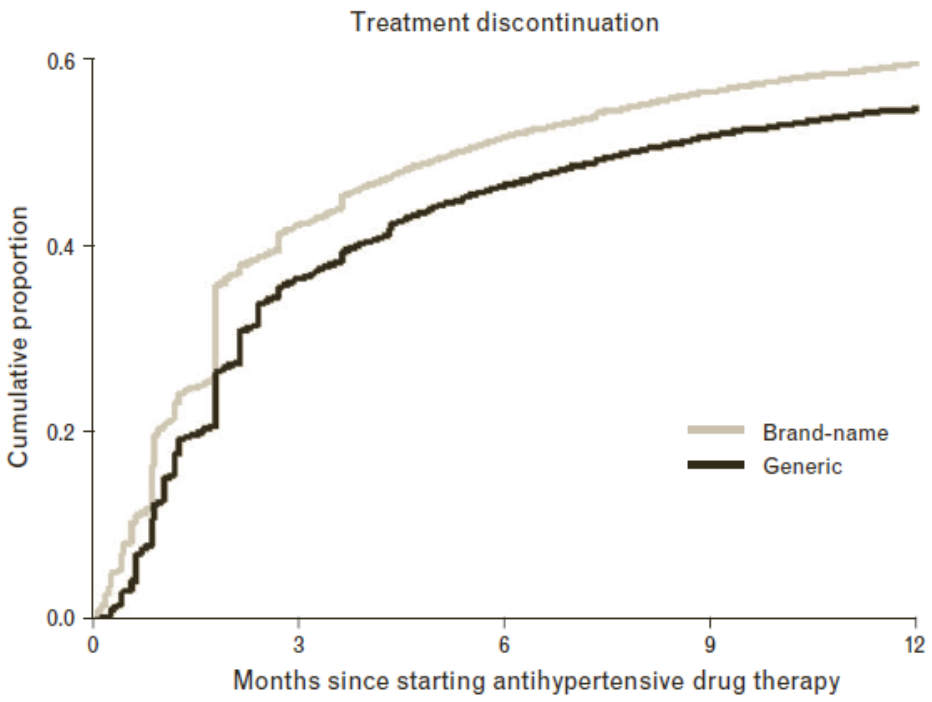


FIGURE 2 Cumulative proportion of patients discontinuing antihypertensive drug therapy according to whether they start treatment with a brand-name or generic drug.

J Hypertens 32:000–000 2014

Off-Patent Generic Medicines vs. Off-Patent Brand Medicines for Six Reference Drugs: A Retrospective Claims Data Study from Five Local Healthcare Units in the Lombardy Region of Italy

Giorgio L. Colombo[1,2*], Enrico Agabiti-Rosei[3], Alberto Margonato[4], Claudio Mencacci[5], Carlo Maurizio Montecucco[6], Roberto Trevisan[7]

Table 2. Analysis of persistence in therapy: continuation of therapy (DDD duration) for the recommended period of time.

	GAP	Type	No.	Min	ASL associated with min	Max	ASL associated with max	Mean Diff.	SD	CI 95% Low. Lim.	CI 95% Upp. Lim.	p-value
Metformin	90 days	Branded	6410	305.7	Milano city	435.5	Lecco	67.23	6.56	54.38	80.08	<0.0001
A10BA02		Generic	7688	254.3	Lecco	508.4	Melegnano					
Amlodipine	90 days	Branded	11435	367.8	Milano city	441.9	Bergamo	78.69	6.74	65.47	91.91	<0.0001
C08CA01		Generic	5101	441.6	Milano city	535.5	Bergamo					
Simvastatin	90 days	Branded	6355	281.15	Milano city	365.2	Melegnano	79.79	5.89	68.25	91.33	<0.0001
C10AA01		Generic	10133	348.7	Milano city	428.1	Melegnano					
Sertraline	30 days	Branded	3822	144.9	Milano city	183.1	Melegnano	23.48	5.21	13.28	33.68	<0.0001
N06AB06		Generic	3176	119.2	Lecco	231.7	Melegnano					
Propafenone	30 days	Branded	805	197.1	Milano city	291.9	Bergamo	9.07	21.08	−32.24	50.39	N.S.
C01BC03		Generic	328	137.5	Lecco	274.0	Bergamo					
Alendronate	60 days	Branded	1821	281.4	Pavia	369.1	Melegnano	41.07	11.66	18.22	63.91	0.0004
M05BA04		Generic	1605	328.1	Milano city	401.1	Lecco					

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Off-Patent Generic Medicines vs. Off-Patent Brand Medicines for Six Reference Drugs: A Retrospective Claims Data Study from Five Local Healthcare Units in the Lombardy Region of Italy

Giorgio L. Colombo[1,2]*, Enrico Agabiti-Rosei[3], Alberto Margonato[4], Claudio Mencacci[5], Carlo Maurizio Montecucco[6], Roberto Trevisan[7]

Table 3. Analysis of patients' compliance for persistent patients (MPR - Medical Possession Ratio).

	Type	No.	Min	ASL associated with min	Max	ASL associated with max	Mean Diff.	SD	CI 95% Low. Lim.	CI 95% Upp. Lim.	p-value
Metformin	Branded	6410	0.47	Milano city	0.55	Lecco	0.03	0.01	0.02	0.04	<0.0001
A10BA02	Generic	7688	0.46	Lecco	0.58	Melegnano					
Amlodipine	Branded	11435	0.75	Milano city	0.84	Melegnano	0.04	0.01	0.04	0.05	<0.0001
C08CA01	Generic	5101	0.79	Milano city	0.87	Melegnano					
Simvastatin	Branded	6355	0.42	Milano city	0.48	Melegnano e Lecco	0.03	0.01	0.02	0.04	<0.0001
C10AA01	Generic	10133	0.45	Milano city	0.50	Melegnano					
Sertraline	Branded	3822	0.63	Milano city	0.68	Bergamo e Melegnano	0.03	0.01	0.01	0.04	0.0003
N06AB06	Generic	3176	0.63	Lecco	0.72	Melegnano					
Propafenone	Branded	805	0.62	Milano city	0.72	Melegnano	0.04	0.02	−0.01	0.08	N.S.
C01BC03	Generic	328	0.65	Lecco	0.83	Melegnano					
Alendronate	Branded	1821	0.68	Lecco e Pavia	0.73	Melegnano	0.01	0.01	−0.01	0.03	N.S.
M05BA04	Generic	1605	0.69	Milano city	0.74	Bergamo					

ASL: Local Healthcare Units. ASLs enrolled: Milano city; Lecco; Bergamo; Pavia; Milano2.
DDD: Defined Daily Dose.
N.S. not statistically significant.

$$\mathrm{MPR} = \frac{(\text{number of packs in the period of persistence}) \times (\text{number of DDDs per pack})}{\text{total days until change of therapy}}$$

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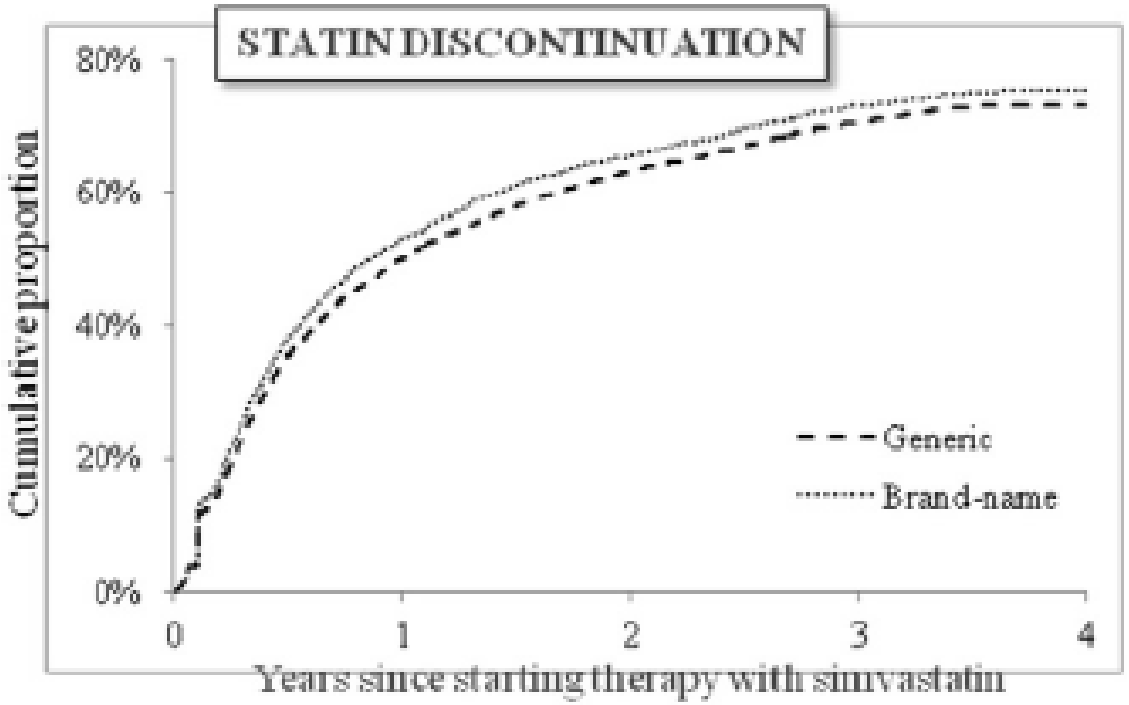

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Original Article

Are generic and brand-name statins clinically equivalent? Evidence from a real data-base

Giovanni Corrao [a,*], Davide Soranna [a,b], Andrea Arfè [a], Manuela Casula [c], Elena Tragni [c], Luca Merlino [d], Giuseppe Mancia [b,e], Alberico L. Catapano [c,f]

Cumulative proportion of patients discontinuing therapy, upper panel, and experiencing hospitalization for major cardiovascular events, below panel

Pharmacy Benefits and the Use of Drugs by the Chronically Ill

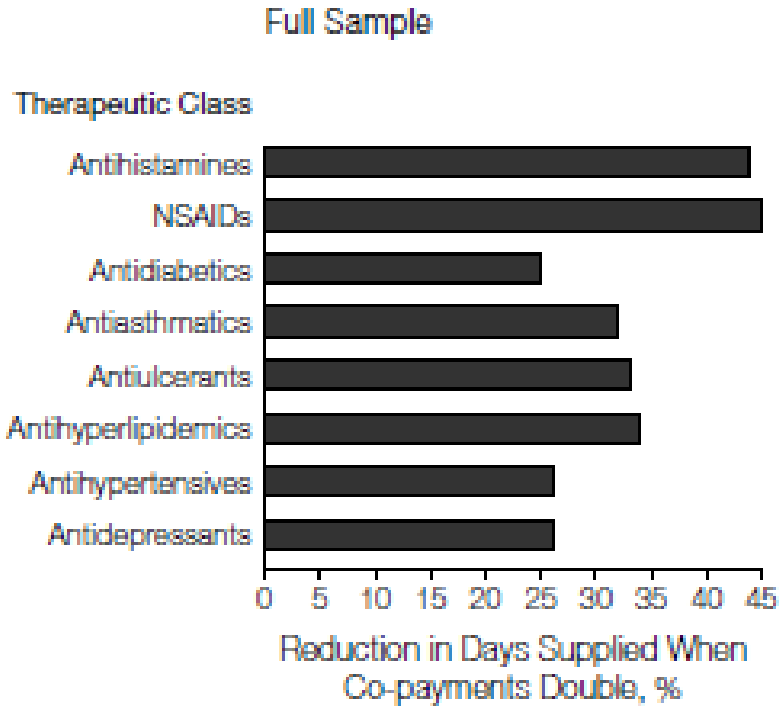
Dana P. Goldman, PhD
Geoffrey F. Joyce, PhD
Jose J. Escarce, MD, PhD
Jennifer E. Pace, BS
Matthew D. Solomon, MA
Marianne Laouri, PhD
Pamela B. Landsman, MPH, DrPH
Steven M. Teutsch, MD, MPH

Context Many health plans have instituted more cost sharing to discourage use of more expensive pharmaceuticals and to reduce drug spending.

Objective To determine how changes in cost sharing affect use of the most commonly used drug classes among the privately insured and the chronically ill.

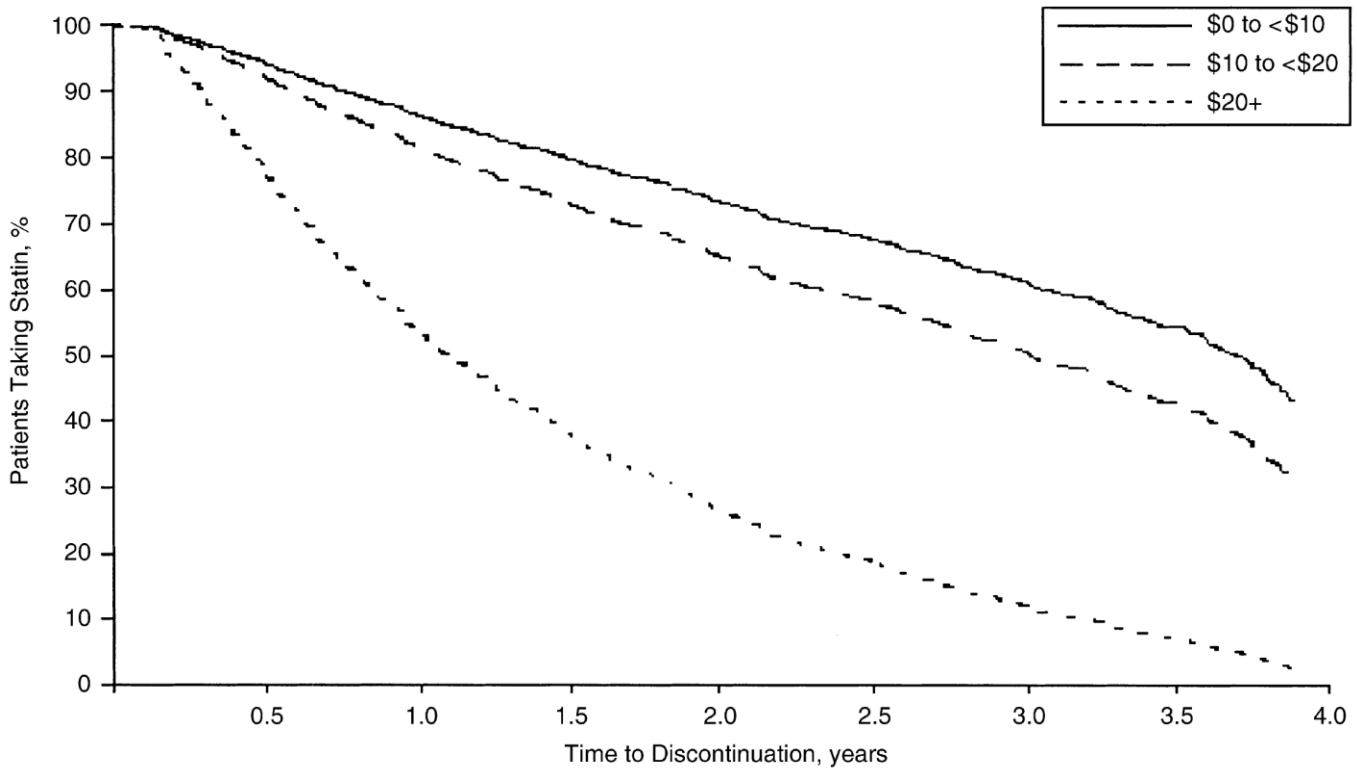
Design, Setting, and Participants Retrospective US study conducted from 1997 to 2000, examining linked pharmacy claims data with health plan benefit designs from 30 employers and 52 health plans. Participants were 528969 privately insured beneficiaries aged 18 to 64 years and enrolled from 1 to 4 years (960791 person-years).

Main Outcome Measure Relative change in drug days supplied (per member, per year) when co-payments doubled in a prototypical drug benefit plan.



JAMA. 2004;291:2344-2350

Survival curves for discontinuation of statin therapy by range of mean prescription copayment



Switch branded to generics?

- Differences in terms of compliance

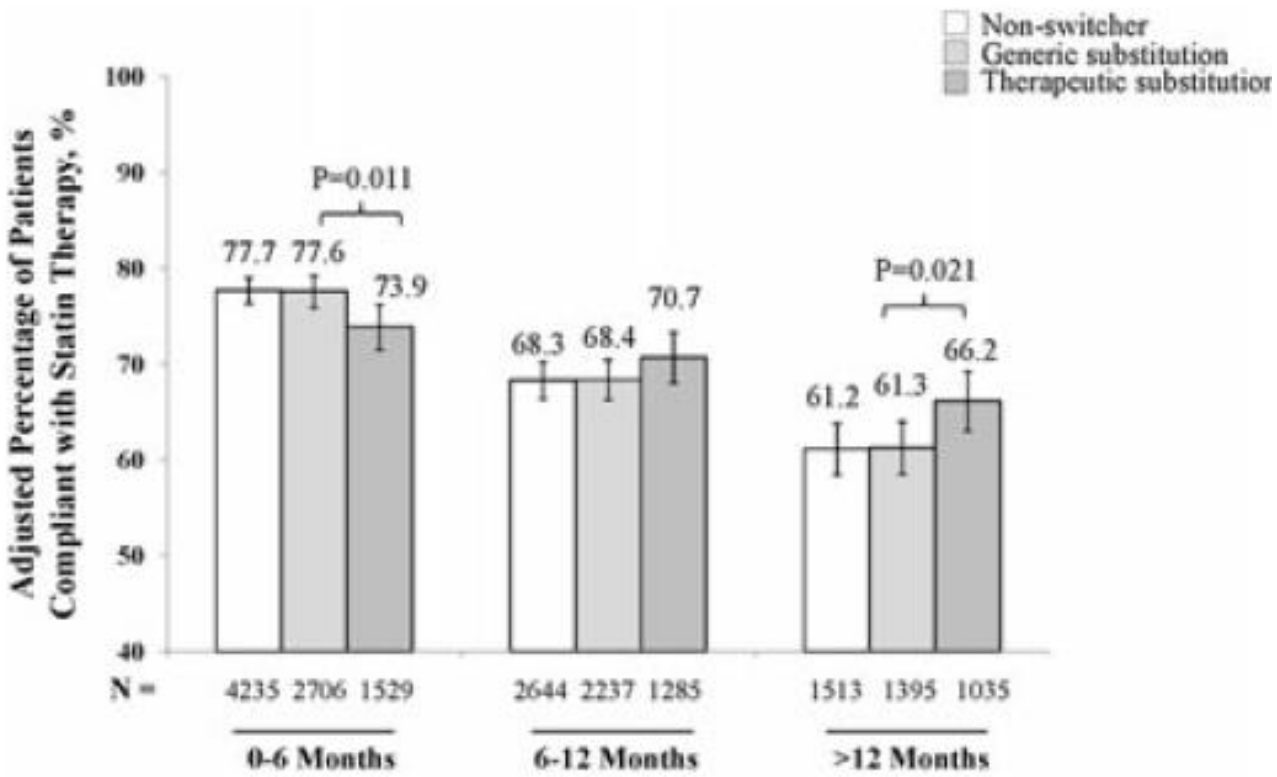


Figure 3. Adjusted percentage of patients compliant with statin therapy from index date by substitution-type subgroups. Percentages were adjusted for variables included in propensity score, duration of post-index statin therapy, and statin days supply. Error bars represent 95% confidence inter-

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2014; **23**: 1093–1100
Published online 9 May 2014 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3630

ORIGINAL REPORT

Compliance after switching from branded to generic statins

Robert J. Romanelli[1,2]*, Trevor Jukes[1] and Jodi B. Segal[3]

CMAJ OPEN

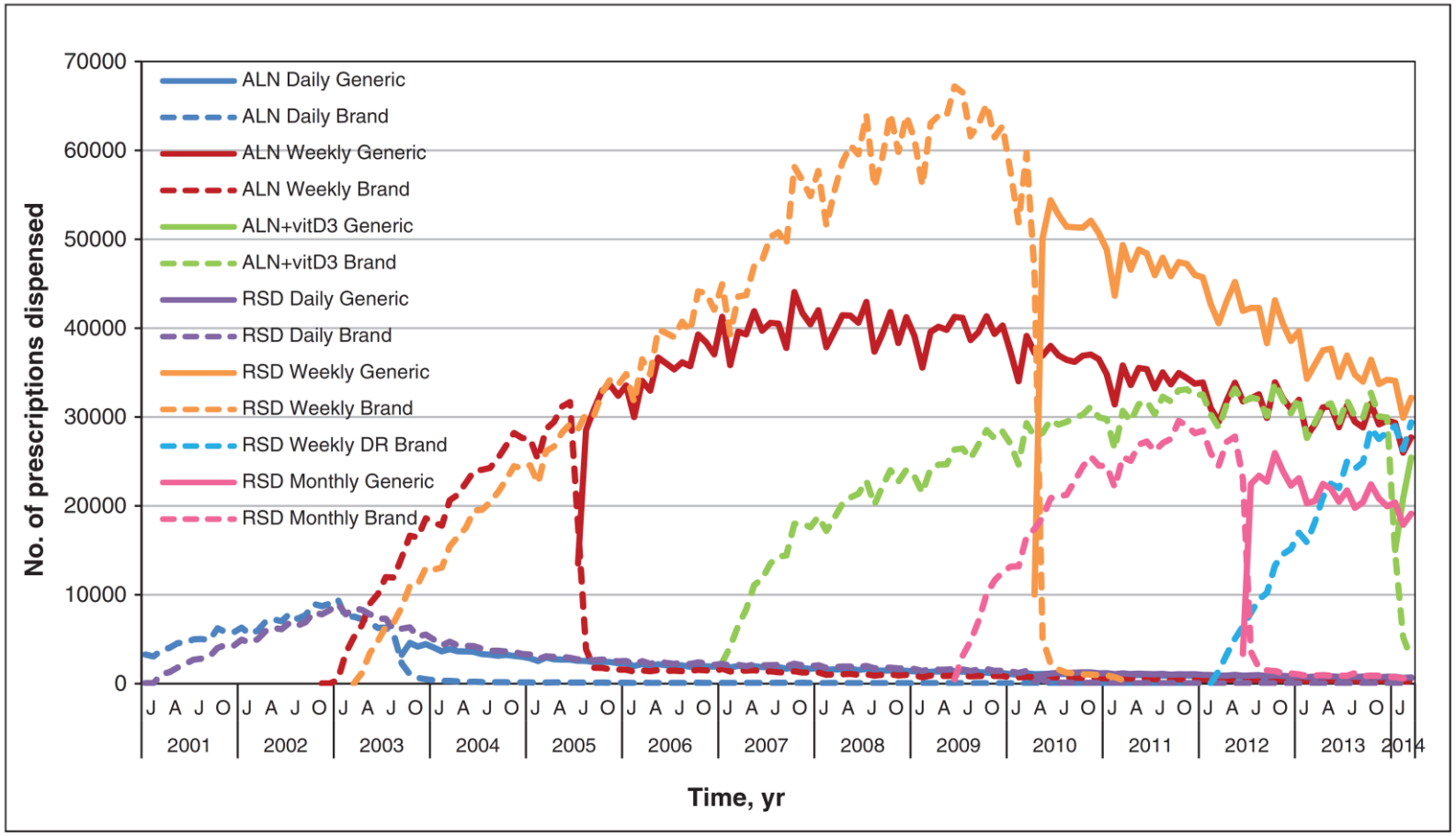
Research

Patterns of use for brand-name versus generic oral bisphosphonate drugs in Ontario over a 13-year period: a descriptive study

Lisa-Ann Fraser MD MSc, Jordan M. Albaum MSc, Mina Tadrous PharmD MS, Andrea M. Burden BSc, Salimah Z. Shariff PhD, Suzanne M. Cadarette PhD

CMAJ Open 2015. DOI:10.9778/cmajo.20140090

Number of brand-name and generic bisphosphonate prescriptions dispensed from pharmacies



ALN = alendronate, vitD3 = vitamin D3, RSD = risedronate, DR = delayed release, Ca = calcium

CMAJ Open 2015. DOI:10.9778/cmajo.20140090

Conclusion of the study

Our study provides evidence that an automatic generic substitution policy, when feasible, is a rapid and effective way to change dispensing patterns.

Currently, 45% of all drugs dispensed by pharmacies in Canada and most drugs used in hospital are generics.

In the United States, generic drug use resulted in $1.2 trillion in savings to the health care system from 2003 to 2012.

Savings increased by an average of 17% per year since 2007 and are expected to grow exponentially as multiple high-use drug patents will expire in the near future.

CMAJ Open 2015. DOI:10.9778/cmajo.20140090

Switch between generics?

- <u>Differences in terms of:</u>

- Compliance
- Adherence
- Efficacy

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Atherosclerosis Supplements xx (2016) 1–8

ATHEROSCLEROSIS
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Impact of substitution among generic drugs on persistence and adherence: A retrospective claims data study from 2 Local Healthcare Units in the Lombardy Region of Italy

Giorgio L. Colombo [c], Enrico Agabiti-Rosei [b], Alberto Margonato [d], Claudio Mencacci [e], Carlo Maurizio Montecucco [f], Roberto Trevisan [g], Alberico L. Catapano [a,*]

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[b] *Division of Medicine and Surgery, Spedali Civili, Brescia, Italy*
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[e] *Department of Neuroscience, A.O. Fatebenefratelli e Oftalmico, Milan, Italy*
[f] *Division of Rheumatology, IRCCS Policlinico S Matteo, University of Pavia, Italy*
[g] *Unit of Diabetology, Ospedali Riuniti di Bergamo, Bergamo, Italy*

Table 1
Number and percentage of patients with no substitution or with at least 1 substitution of generic drugs during the observation period by therapeutic area and by ASL.

Therapeutic area	ASL Bergamo				ASL Pavia			
	No substitution		At least one substitution		No substitution		At least one substitution	
	N	%	N	%	N	%	N	%
Diabetes	1754	45.68	2086	54.32	903	39.66	1374	60.34
Dyslipidemia	1907	41.99	2635	58.01	1154	33.12	2330	66.88
Hypertension	1063	35.77	1909	64.23	996	30.68	2250	69.32
Osteoporosis	273	48.66	288	51.34	187	42.12	257	57.88
Psychiatry	572	44.44	715	55.56	405	36.16	715	63.84
Total	5569	42.18	7633	57.82	3645	34.48	6926	65.52

Colombo G-L et al Atherosclerosis Supplements (In press) (2016) 1-8

Table 2
mean frequency of substitutions by therapeutic areas and by ASL.

Therapeutic area	ASL Bergamo			ASL Pavia		
	N	Mean	SD	N	Mean	SD
Diabetes	3840	0.17	0.24	2277	0.19	0.25
Dyslipidemia	4542	0.26	0.31	3484	0.29	0.32
Hypertension	2972	0.27	0.31	3246	0.30	0.31
Osteoporosis	561	0.22	0.29	444	0.25	0.30
Psychiatry	1287	0.33	0.38	1120	0.33	0.36

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Table 3
Persistence of treatment stratified by generic substitution class, therapeutic area and by ASL.

Therapeutic area	Substitution frequency classes	Persistence (days)					
		ASL Bergamo			ASL Pavia		
		N	Mean	SD	N	Mean	SD
Diabetes	Range (1%–15%)	605	984.64	212.29	457	988.50	263.98
	Range (15%–30%)	595	851.60	316.78	359	867.90	344.50
	Range (30%–45%)	413	782.51	359.58	257	694.99	398.36
	Range (45%–60%)	232	605.50	413.74	117	747.40	401.98
	Range (≥60%)	241	310.51	315.76	184	352.60	355.20
Dyslipidemia	Range (1%–15%)	430	980.66	209.82	410	890.48	319.53
	Range (15%–30%)	586	820.88	311.35	561	758.15	376.38
	Range (30%–45%)	477	750.85	348.65	465	615.14	400.90
	Range (45%–60%)	410	585.23	401.08	251	595.97	412.08
	Range (≥60%)	732	371.79	357.76	643	407.06	374.70
Hypertension	Range (1%–15%)	369	1021.12	196.89	384	988.09	302.92
	Range (15%–30%)	429	882.48	314.32	537	817.60	366.28
	Range (30%–45%)	364	782.72	364.22	406	710.08	396.75
	Range (45%–60%)	306	615.38	406.90	325	696.23	405.76
	Range (≥60%)	441	401.58	374.06	598	448.23	381.11
Osteoporosis	Range (1%–15%)	36	969.28	218.82	37	817.51	350.82
	Range (15%–30%)	77	710.52	345.12	66	734.36	359.42
	Range (30%–45%)	63	710.76	353.06	48	515.17	410.43
	Range (45%–60%)	48	503.00	377.09	43	514.81	391.46
	Range (≥60%)	64	367.63	343.12	63	375.24	331.00
Psychiatry	Range (1%–15%)	56	815.07	291.03	81	841.30	354.41
	Range (15%–30%)	106	566.19	326.88	139	660.93	399.34
	Range (30%–45%)	96	481.77	360.16	130	457.92	320.43
	Range (45%–60%)	131	320.36	280.15	85	359.11	338.91
	Range (≥60%)	326	197.78	171.33	280	247.45	252.37

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Table 4

Adherence to treatment stratified by generic substitution class, therapeutic area and by ASL.

Therapeutic area	Substitution frequency classes	MPR					
		ASL Bergamo			ASL Pavia		
		N	Mean	SD	N	Mean	SD
Diabetes	Range (1%–15%)	605	0.68	0.23	457	0.84	0.21
	Range (15%–30%)	595	0.65	0.25	359	0.76	0.25
	Range (30%–45%)	413	0.64	0.25	257	0.71	0.27
	Range (45%–60%)	232	0.61	0.27	117	0.68	0.28
	Range (≥60%)	241	0.50	0.28	184	0.60	0.30
Dyslipidemia	Range (1%–15%)	430	0.66	0.20	410	0.83	0.22
	Range (15%–30%)	586	0.59	0.20	561	0.77	0.25
	Range (30%–45%)	477	0.58	0.21	465	0.67	0.28
	Range (45%–60%)	410	0.52	0.22	251	0.53	0.22
	Range (≥60%)	732	0.46	0.24	643	0.49	0.24
Hypertension	Range (1%–15%)	369	0.96	0.09	384	0.98	0.06
	Range (15%–30%)	429	0.93	0.14	537	0.96	0.11
	Range (30%–45%)	364	0.91	0.15	406	0.94	0.13
	Range (45%–60%)	306	0.90	0.16	325	0.91	0.15
	Range (>60%)	441	0.81	0.24	598	0.85	0.21
Osteoporosis	Range (1%–15%)	36	0.92	0.09	37	0.98	0.05
	Range (15%–30%)	77	0.86	0.15	66	0.93	0.11
	Range (30%–45%)	63	0.88	0.12	48	0.84	0.21
	Range (45%–60%)	48	0.77	0.21	43	0.81	0.22
	Range (>60%)	64	0.71	0.27	63	0.71	0.26
Psychiatry	Range (1%–15%)	56	0.97	0.09	81	0.98	0.07
	Range (15%–30%)	106	0.93	0.12	139	0.96	0.12
	Range (30%–45%)	96	0.89	0.18	130	0.91	0.16
	Range (45%–60%)	131	0.80	0.25	85	0.82	0.24
	Range (≥60%)	326	0.78	0.25	280	0.78	0.28

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Correlation between persistance and adherence to treatment and generic distribution

Table 5
Correlation between persistence and adherence to treatment and generic substitution stratified therapeutic area and by ASL.

Therapeutic area	Persistence				MPR			
	Bergamo		Pavia		Bergamo		Pavia	
	Pearson corr. Coeff.	p-value	Pearson corr. Coeff.	p-value	Pearson corr. Coeff.	p-value	Pearson corr. Coeff.	p-value
Diabetes	−0.45005	<0.0001	−0.47038	<0.0001	−0.17708	<0.0001	−0.30642	<0.0001
Dyslipidemia	−0.56764	<0.0001	−0.48464	<0.0001	−0.32662	<0.0001	−0.47813	<0.0001
Hypertension	−0.53508	<0.0001	−0.49124	<0.0001	−0.27340	<0.0001	−0.38135	<0.0001
Osteoporosis	−0.51589	<0.0001	−0.46460	<0.0001	−0.30139	<0.0001	−0.50583	<0.0001
Psychiatry	−0.68829	<0.0001	−0.64439	<0.0001	−0.30457	<0.0001	−0.40548	<0.0001

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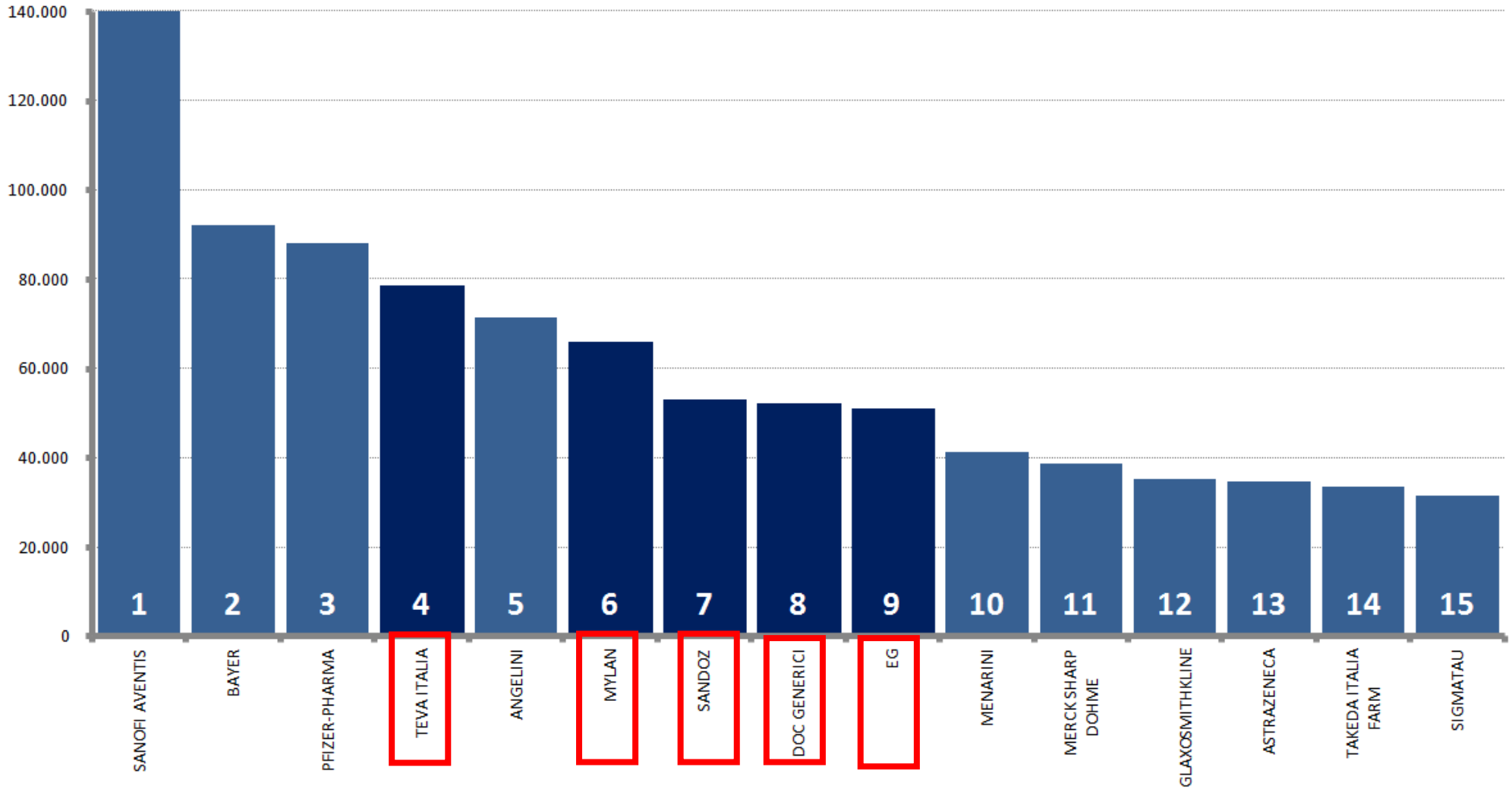
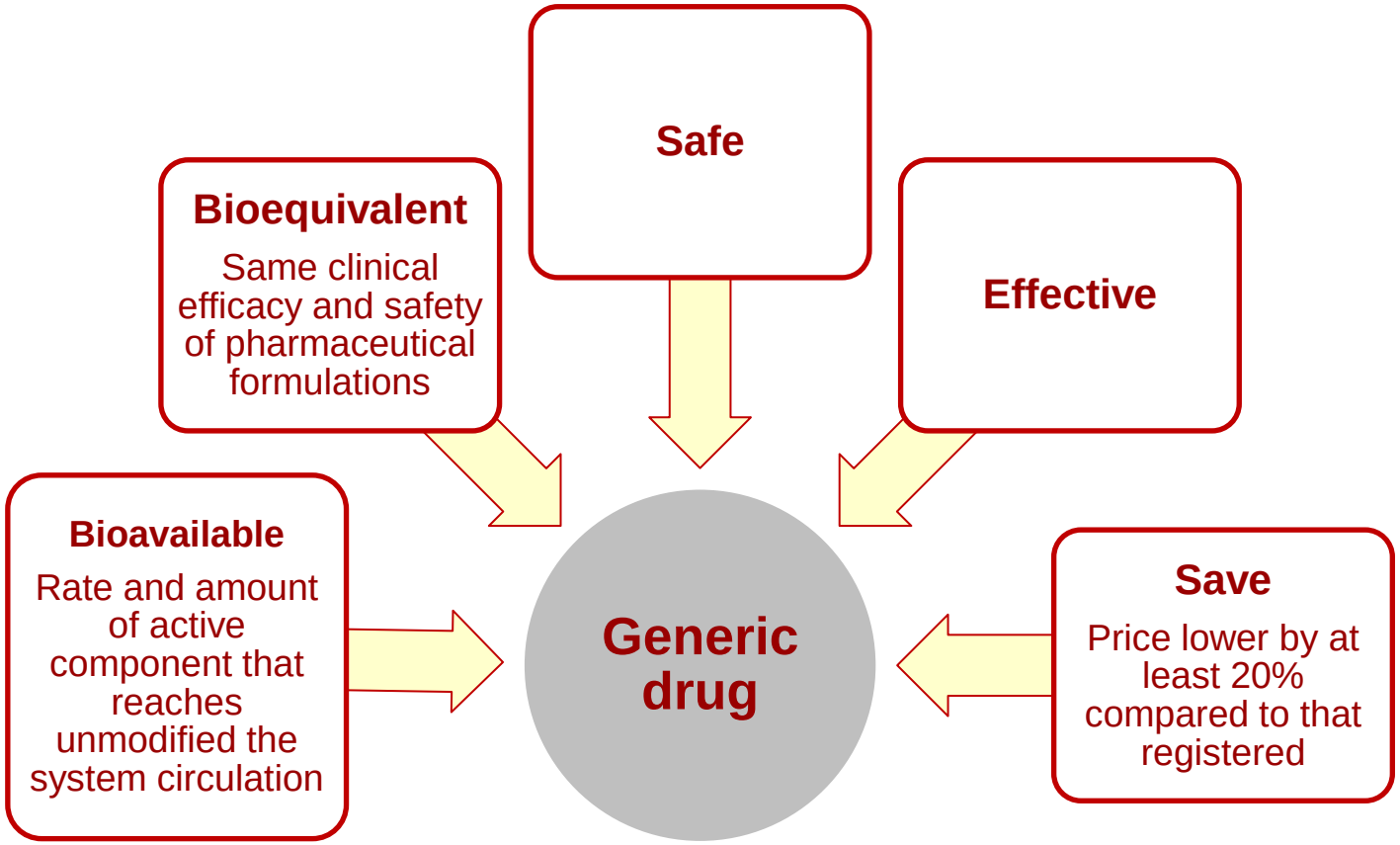
5. Conclusions

Substitution among generic drugs with different formulations and appearance is feasible. The higher the frequency of substitutions, the shorter the persistence and adherence with therapy. The impact of frequent substitutions on persistence and adherence, which may influence efficacy and/or safety should therefore be monitored and if possible avoided. Given the clinical and economic benefits of better adherence and persistence with therapy, targeting interventions to patients who are at high risk for non-adherence and early discontinuation, should be an important part of medication therapy in chronic diseases [2,33,34,38].

Main pharmaceutical companies



Fonte: Rielaborazioni Centro Studi Assogenerici, su dati IMS Health MAT 03/2014


Safe
Bioequivalent
Same clinical efficacy and safety of pharmaceutical formulations
Effective
Bioavailable
Rate and amount of active component that reaches unmodified the system circulation
Generic drug
Save
Price lower by at least 20% compared to that registered